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HEIGHT AND WEIGHT IN RELATION TO ONSET OF PUBERTY IN BOYS

BY

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The great majority of studies of growth in relation to puberty have been carried out on girls, since the onset of menstruation provides a fixed point which can be accurately recorded, whilst the age of establishment of a regular menstrual cycle can also be determined in most cases within comparatively narrow limits. Although the onset of menstruation does not necessarily correspond with the onset of ovulation, and has indeed tended to obscure the fact that puberty is actually a period of transition from childhood to adolescence rather than a single fixed point, its use for statistical purposes has thrown considerable light on the relationship of growth to early or late maturity. Thus Flory (1935) and others have found that girls who menstruated early showed radiological evidence of more advanced osseous development (e.g. appearance of the sesamoid on the distal end of the first metacarpal) than non-pubescent children of the same age, whilst Stone and Barker (1937) described an early slowing-down of growth in girls who had menstruated early, and found that, after the age of sixteen, girls who had not menstruated were in fact taller than those in whom the menarche had occurred.

In the case of boys there is no fixed point corresponding to the onset of menstruation which can be accurately determined, and it is probable that spermatogenesis is more gradually established than ovulation. Assays of excretion of 17-ketasteroids (Nathanson et al., 1939, 1941; Talbot et al., 1943) also suggest that this is of gradual increase, with a wide normal variation, and although excretion of gonadotrophic hormone in the urine shows a general tendency to increase with increasing maturity (Catchpole et al., 1938) it cannot as yet be said to provide an accurate index of onset of puberty. The appearance of pubic hair, though usually an early sign of pubescence, bears no very constant relationship to genital development, whilst other secondary sexual characters, e.g. skin and voice changes, are all gradual in onset.

By considering the various clinical manifestations of puberty together, however, it is possible even in boys to establish grades of maturity, and to classify groups of boys into these with some degree of accuracy. Greulich et al. (1942) have described five such maturity-groups. Although the classical monograph of these authors was not available when the present study was carried out, it was found subsequently that closely similar criteria for grading had been established independently; in the present study, however, only three maturity-groups have been compared, the 'prepubescent' group corresponding approximately with Greulich's Grades 1 and 2, the 'pubescent' with Grade 3, and the 'adolescent' with Grades 4 and 5.

The purpose of the present investigation was to determine whether any significant difference in mean height and weight of boys in the same age-groups but in different maturity-groups could be demonstrated and, if so, how far back these differences were manifest. At the same time it was possible to make certain observations on the order of appearance and character of some of the changes associated with puberty.

Present Investigation

Clinical material. This consisted of two hundred and eight healthy boys between the ages of eleven and sixteen years. All boys who had had prolonged or recent illness likely to have affected their growth were excluded, as were any showing cryptorchidism. No other cases of endocrine disturbance or pathological obesity were encountered. The boys were derived from two residential schools, in both cases situated in country surroundings and providing a liberal diet. In all cases, detailed medical records were available.

In School A, the boys entered from foster-homes at the age of five, being weighed and measured by trained personnel on entry and thereafter in January of each year, or more frequently. Until 1945, all the boys had remained at school during the holidays, and had received the same school diet. This group was, therefore, exceptionally well controlled from the point of view of an investigation of this type, and measurements were available in every case from the sixth year.

In School B, the boys entered from their homes at various ages from eight years onward, and were weighed and measured by trained personnel at least three times a year. They received the same diet at school, but returned home for the holidays.

Although the living conditions and diet in the two schools were comparable, it was considered best to compare measurements only of boys from the same school. Whilst this renders the individual

groups smaller, it reduces a number of possible errors. Thus the boys in the two schools were derived from somewhat different stock, whilst the social conditions in the immediate pre-school years were probably more uniform in the case of School A than of School B.

Age-groups. The boys were divided into yearly groups, i.e. 11+ to 12, 12+ to 13, etc., a birthday falling on the date of the examination placing the boy in the younger age-group. In the case of School A, where the exact date of each previous measurement was known, the ages were calculated throughout on the basis of years plus days; in the case of School B, where the month but not the exact date of the previous examinations was recorded, ages were calculated to the nearest month. The age-groups examined in the two schools were as follows :

Age (years)	School A	School B
11 to 12	26	—
12 to 13	39	—
13 to 14	45	28
14 to 15	16	28
15 to 16	4	22

Some of these groups were too small, or insufficiently divided on a maturity-grading, to make comparisons possible; the age-groups selected for analysis were 12 to 13 (School A), 13 to 14 (Schools A and B), 14 to 15 (School B), and 15 to 16 (School B).

Measurements. Heights were measured with the boys standing barefoot against a stationary measure with sliding head-arm, and were recorded either to the nearest ¼ inch (and converted into cm.) or to the nearest 0·5 cm. Leg-length was measured with a steel tape, from the anterior superior iliac spine to the tip of the internal malleolus, and recorded to the nearest 0·5 cm. Weights were measured on lever balances that had been regularly checked, were recorded to the nearest ¼ lb. and converted to the metric scale. All calculations are based on the naked weight.

Examination. A record was made of the presence and extent of pubic, axillary, facial, and body hair; the stage of development of the genitalia; and the appearance of the skin, with particular reference to the presence of comedones or acne and the development of the sebaceous and apocrine sweat glands. It was not found practicable to estimate early changes in the pitch of the voice on a single examination or without special apparatus, though in those cases where the voice was obviously 'broken' the fact was recorded. The presence or absence of gynaecomastia was noted in all cases.

PUBIC HAIR. This was recorded as P0 when the pubic area showed only the presence of the fine body-hair of early childhood, or the slightly longer, non-pigmented vellus which precedes the appearance of true pubic hair. P1 was used to describe the appearance of one or more coarse, pigmented hairs at the base or sides of the penis; P2 when pigmented hairs extended across the root of the penis; P3 when approximately half the pubis was covered; P4 when the area of female distribution was covered, and hairs extended to the perineal or anal region; and P5 when hair was present on the linea alba, lower abdomen, or groins (cf. Godin, 1934).

AXILLARY HAIR. This was recorded as A0 (complete absence), A1 (the presence of one or more pigmented hairs), A2 (hairs more than 1 cm. in length and extending over an area approximately 2 cm. in length), or A3 when the growth of axillary hair was profuse.

FACIAL HAIR. The significance of facial hair was found less easy to assess, since the appearance was greatly influenced by colouring or shaving. Typically the earliest appearance of fine hair was seen on the lateral parts of the upper lip, thence spreading toward the centre. Except in the most hirsute boys, it was only found practicable to classify facial hair as present or absent.

BODY HAIR. The posterior aspects of the forearms were examined for hair-growth, but it was again found that only in the most mature boys were the findings unequivocal.

GENITALIA. Greulich et al. (1942) drew attention to three features of the male genitalia at puberty, which were also used as criteria of maturity-grading in the present study. The penis first increases considerably in length, and then subsequently in girth with development of the corpora cavernosa. The rapid increase in size of the testicles at puberty is not associated with a corresponding increase in size of the epididymis, with the result that the relative proportions of the two show a marked alteration from those of childhood; with increase in size the testicles also become softer. Thirdly, the scrotum, which in childhood is widest at its proximal end, becomes not only pendulous but wider at its distal end with the increased size of the testicles. (This last point was found easier to assess clinically than rugosity, which was very variable.)

In the present study, the stage of development of the penis and that of the testicles plus scrotum were separately assessed as 'prepubescent,' 'pubescent,' or 'adolescent.' (It was found that whereas the development of the scrotum followed closely that of the testicles, the testicles and penis were not necessarily developed to an equal extent.)

SKIN. The skin of the cheeks, roots of the nose, and base of the lower lip was examined for comedones, and though their presence was found to be much higher after the onset of puberty, it was not itself taken as a criterion of diagnosis. The group as a whole was remarkably free from acne, and though the few cases that were observed were all in the more mature boys, its presence or absence was of little help in grading. Development of the apocrine and sebaceous glands was also regarded as confirmatory rather than diagnostic.

GRADING. On the basis of the clinical examination, irrespective of age and size, each boy was graded as 'prepubescent,' 'pubescent,' or 'adolescent.' The presence of pubic hair and/or pubescent genital development were taken as the criteria of pubescence. The presence of pubic hair, even when this was profuse, was not by itself taken as a criterion of adolescence ; for this grading, well-marked increase in girth as well as length of the penis, and substantial development of the testicles were considered necessary.

In spite of the inherent difficulties which must arise over border-line cases (since one stage of development will pass gradually and not abruptly to the next), it appeared that grading on this basis was substantially valid. A second examination of a hundred and thirty-two of the boys was carried out one hundred days after the first, and a second assessment made without reference to the original one. It was found that in no instance was a boy given a lower grading on his second examination than on his

first; eleven boys were given a higher grading in view of the advanced development that had occurred during the interval; and the remainder were placed in the same categories as before.

Results

Maturity in relation to age. The following analysis of the total number of boys examined (208) shows how the maturity-gradings are related to chronological age (table 1). As would be expected, the percentage of prepubescent boys steadily falls from the age of 11 to 15, whilst the percentage of adolescents rises from 13 to 16. The highest percentage of pubescent boys is seen in the 13- to 14-year-old group, which is also the group most evenly divided between prepubescent and pubescent.

Comparison of height and weight of maturity groups. In each of the age-groups selected, a comparison was made between the mean height and weight of those boys showing a more advanced degree of maturity with those showing less. Thus in the 12- to 13-year-old group (School A), the mean heights and weights of the 25 prepubescent boys were compared with those of the 14 pubescent boys. In the 13- to 14-year-old groups (Schools A and B), comparison was also made between the prepubescent boys and the pubescent, whilst in the 14- to 15-year-old and 15- to 16-year-old groups (School B), comparison was made between the pubescent and adolescent groups. This initial comparison gave the results shown in table 2.

The probable errors were calculated for each comparison, and it will be seen from table 3 that the probability of the lower maturity-group being of greater height or weight than the higher maturity-group of the same age is in no instance more than 1 in 10, whilst in most instances it is considerably less.

It is thus clear from table 2 that the more mature boys are significantly taller and heavier than the less mature boys in the same age-group. Indeed, the more mature boys in each age-group are found to be taller and heavier than the less mature boys in the age-group immediately above them (e.g. the pubescent boys aged 12 to 13 compared to the prepubescent boys aged 13 to 14, or the adolescent boys aged 14 to 15 compared with the pubescent boys aged 15 to 16). Further evidence that these differences in height and weight between boys of different grades of maturity in the same age-group cannot be attributed to such minor differences in mean age as existed between the maturity-groups is shown by reference to the growth curves given below, where the

TABLE 1

MATURITY IN RELATION TO AGE

Age (years)	Total	Prepubescent		Pubescent		Adolescent	
		No.	Per cent.	No.	Per cent.	No.	Per cent.
11 to 12	26	23	88·5	3	11·5	0	0
12 to 13	39	25	64·1	14	35·9	0	0
13 to 14	73	31	42·5	34	46·6	8	11·0
14 to 15	44	6	13·6	11	25·0	27	61·4
15 to 16	26	0	0	8	30·8	18	69·2

TABLE 2

COMPARISON OF HEIGHT AND WEIGHT OF MATURITY GROUPS

Age Group	School	Height (cm.)			Weight (kg.)		
		Mean	Standard error	Standard deviation	Mean	Standard error	Standard deviation
12 to 13 years							
1. Prepubescent	A	142·10	1·46	5·26	33·32	0·64	3·06
2. Pubescent	A	148·01	1·69	6·09	37·74	1·39	6·66
13 to 14 years							
1. Prepubescent	A	146·30	1·75	7·23	36·30	1·25	5·73
2. Pubescent	A	151·53	1·39	6·93	41·49	1·13	5·63
13 to 14 years							
1. Prepubescent	B	146·53	1·55	5·59	38·33	0·92	3·31
2. Pubescent	B	158·88	1·55	6·20	47·73	1·41	5·64
14 to 15 years							
1. Pubescent	B	155·91	1·19	3·76	46·00	1·12	3·55
2. Adolescent	B	163·83	1·60	6·00	52·18	1·62	6·07
15 to 16 years							
1. Pubescent	B	154·53	2·39	6·76	45·30	2·11	5·96
2. Adolescent	B	164·31	2·74	10·29	53·59	2·14	8·00

TABLE 3

School	Age-group	Probability that prepubescent mean height greater than pubescent mean height	Probability that prepubescent mean weight greater than pubescent mean weight
A	12 to 13	0·015	0·087
A	13 to 14	0·094	0·001
B	13 to 14	0·000	0·000
		Probability that pubescent mean height greater than adolescent mean height	Probability that pubescent mean weight greater than adolescent mean weight
B	15 to 15	0·000	0·005
B	15 to 16	0·004	0·034

mean age of the group at the date of each measurement is shown graphically.

A further point of considerable interest which is brought out by these figures is that the boys who show evidence of the onset of puberty between 13 and 14 years of age (School B), are taller and heavier than those where puberty is beginning between 14 and 15, and these again are taller and heavier than the boys graded as pubescent between 15 and 16 years. Although the differences in this instance are small, the observation suggests that the smallest boys are in fact those that tend to mature the latest.

Growth curves. In view of the above findings, growth curves (height and weight) were constructed for each group, and compared as before. Those for the boys in School A are the more complete, as all boys entered the school in their sixth year. In the case of boys from School B, where the age of entry varied from the eighth to the twelfth year, the curves have been contructed from the age at which they may be taken as representative of the complete group.

It will be seen from these figures that at every age for which mean values are available, the groups of boys who matured earlier are taller and heavier than their later-maturing contemporaries. This is particularly striking in the case of boys from School A (figs. 1 to 4) where the differences are demonstrable in the sixth year. In all cases the curves, particularly those of weight, tend to diverge with the establishment of puberty. Although the individual groups analysed are relatively small, the fact that the findings were similar in every instance tends to support their general validity.

Rate of growth during puberty. The maturity-gradings used in the present study include in the 'prepubescent' group boys whose development is essentially that of childhood, and also those who may show the very earliest signs preceding the more manifest appearances of commencing maturity.

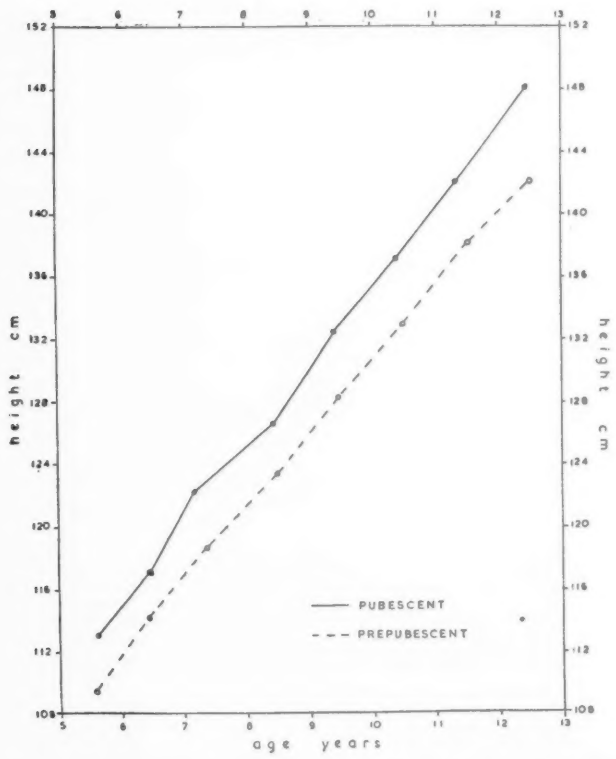

FIG. 1.—Mean height of boys aged 12 to 13 years at date of examination (School A), from the sixth to thirteenth year.

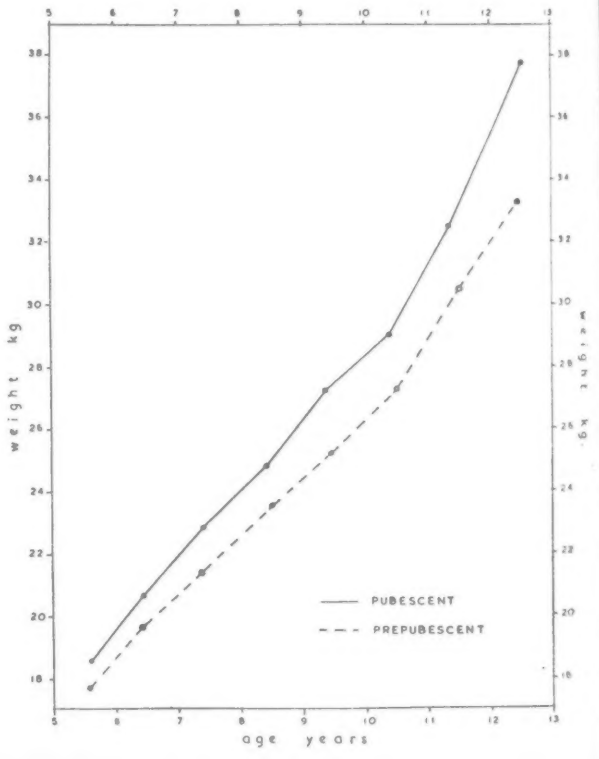

FIG. 2.—Mean weight of boys aged 12 to 13 years at date of examination (School A), from the sixth to thirteenth year.

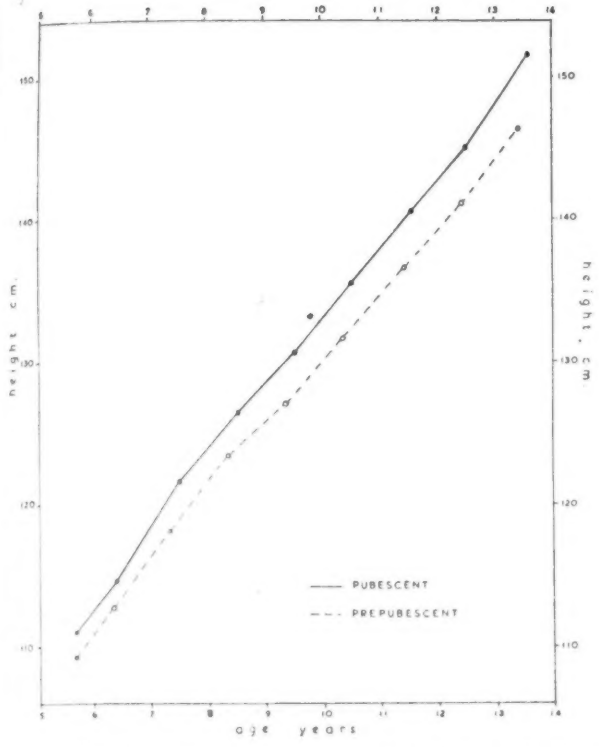

FIG. 3.—Mean height of boys aged 13 to 14 at date of examination (School A), from sixth to fourteenth year.

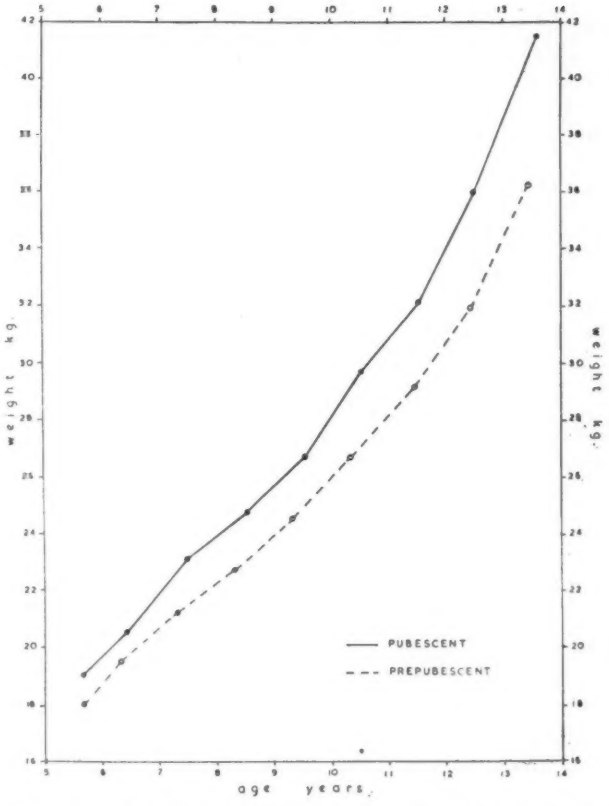

FIG. 4.—Mean weight of boys aged 13 to 14 at date of examination (School A), from sixth to fourteenth year.

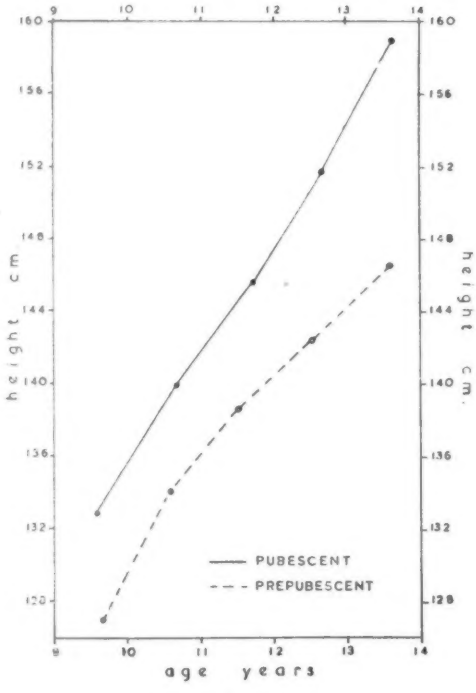

FIG. 5.

FIGS. 5 and 6.—Mean height and weight of boys aged 13 to 14 years at date of examination (School B), from tenth to fourteenth year.

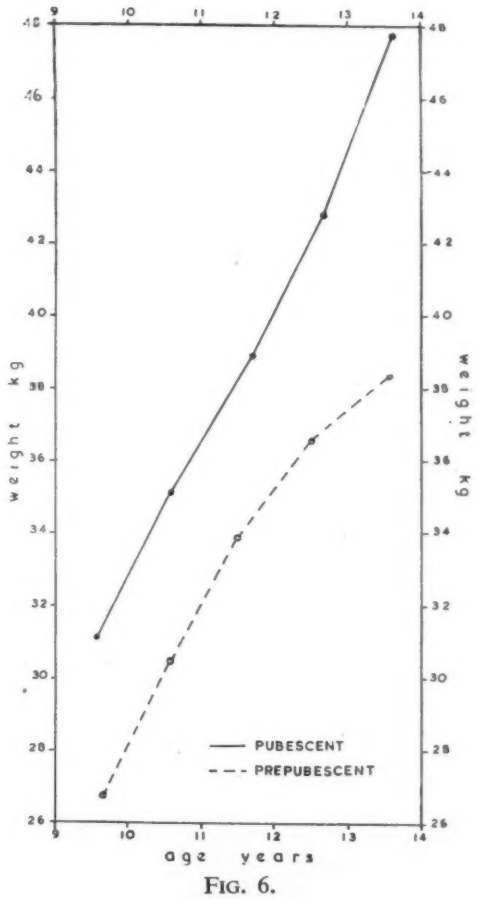

FIG. 6.

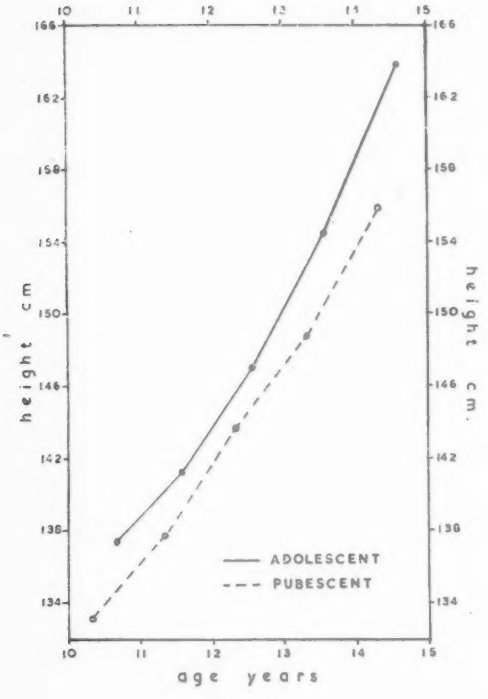

FIG. 7.

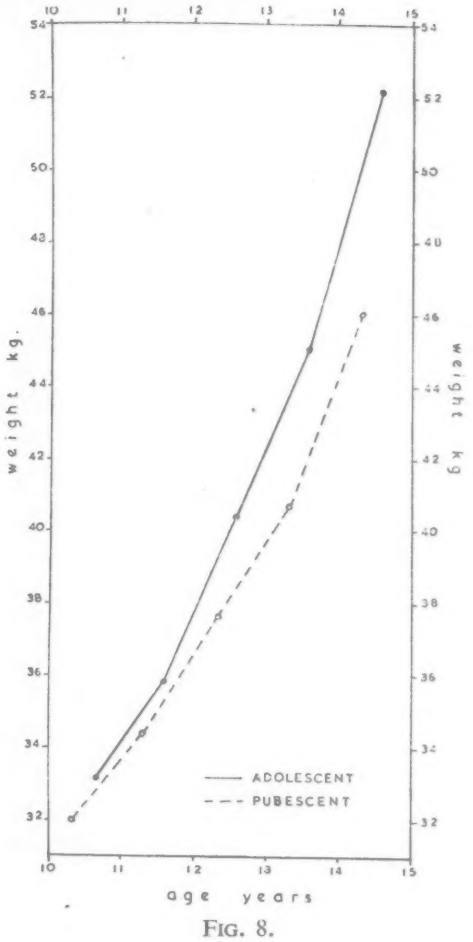

FIG. 8.

FIGS. 7 and 8.—Mean height and weight of boys aged 14 to 15 at date of examination (School B), from eleventh to fifteenth year.

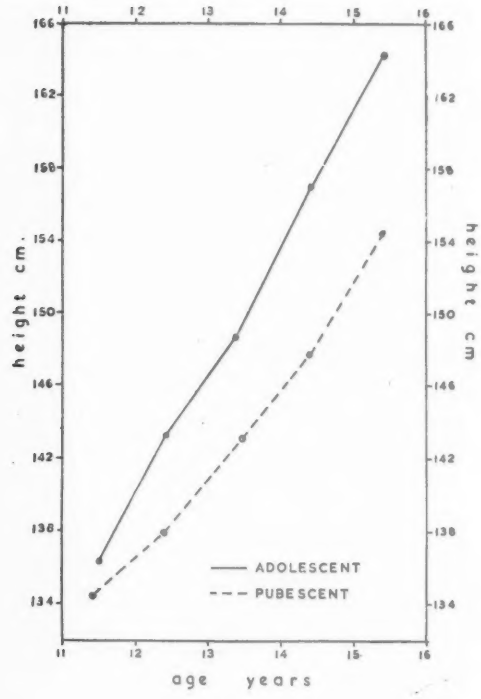

FIG. 9.

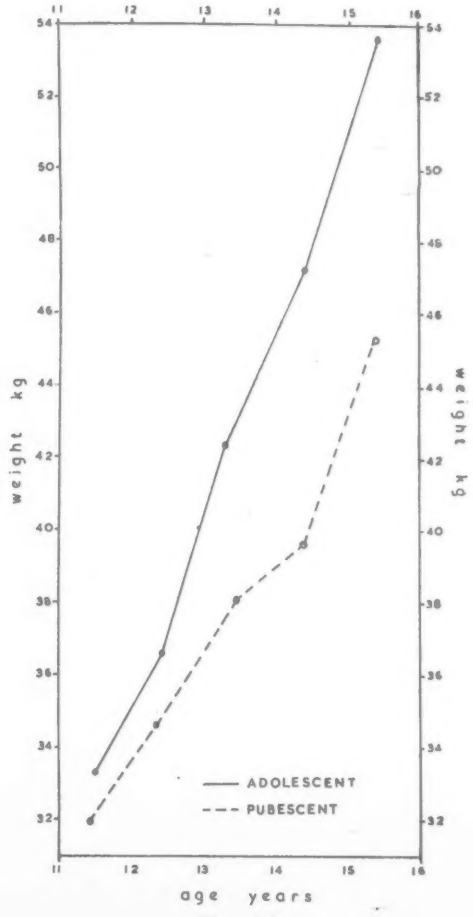

FIG. 10.

FIGS. 9 and 10.—Mean height and weight of boys aged 15 to 16 years at date of examination (School B), from twelfth to to seventeenth year.

The growth curves of the prepubescent boys cannot, therefore, be expected to demonstrate clearly any changes in rate of growth which may be associated with the period immediately preceding the manifestations used in defining the 'pubescent' group. Similarly with the 'adolescent' group, which includes boys in whom maturity is well advanced but incomplete, and also a few boys in whom genital development has practically reached adult proportions, it might reasonably be objected that the grading is too wide to demonstrate changes peculiar to any one phase of development.

In the case of the 'pubescent' group, however, the phase of development is more clearly defined, and probably extends only over a period of six to nine months. Changes in rate of growth peculiar to this period might, therefore, be expected in the growth curves immediately before and after the date of examination. With the exception of the growth in height of the 12- to 13-year-old boys, examination of the growth curves does in fact suggest that there is an access of growth (more particularly in weight) in the year preceding the date of examination. Since, however, a somewhat similar increase in annual weight-gain is seen in the prepubescent boys aged 13 to 14 (School A), it was decided to re-examine this age-group approximately three months after the first examination, in order to determine whether there was any significant difference in the increase in height and weight of the pubescent and prepubescent boys aged 13 to 14 during this period.

The results as shown in table 4 were obtained.

There are, therefore, substantial differences between the increase in height and weight of the pubescent and prepubescent boys over the same period, and since the standard errors are relatively small, these differences can be regarded as significant. (The probability that the increase in height is greater for the prepubescent than for the pubescent boys is approximately 0·10 and in weight only 0·004.) Since, however, the differences in increase in height between the two groups are not shown to the same extent in the increases in leg-length, these results are regarded primarily as an indication that further study along similar lines is likely to be fruitful.

Gynaecomastia. The presence of a small nodule of mammary tissue attached to the nipple (which could readily be distinguished on palpation from subcutaneous fat) was observed in twenty-six cases. In the great majority this was bilateral and painless or only very slightly tender. In no case could colostrum be expressed. In most cases where the mammary tissue was more than 2 cm. in diameter, or where the chest was poorly covered, the swelling was visible as well as palpable, but no very marked case of breast enlargement was observed. The occurrence of gynaecomastia in relation to maturity-grading in the whole group was as follows :

	Total	No. with gynaecomastia.	Per cent.
Prepubescent ..	85	0	0
Pubescent	70	9	12·9
Adolescent ..	53	17	32·1

This would suggest that breast-development is more characteristic of the latter stages of puberty than the earlier, and is unlikely to be observed before other manifestations of sexual development. It is probable that gynaecomastia at puberty is due, as Weber (1946) expresses it, to 'a temporary burst of endocrine activity in the testes and possibly in the adrenal cortex' and that the secretions of these organs contain not only adrogenic but some oestrogenic elements. These latter may be sufficient to produce temporary gynaecomastia in boys who are constitutionally so predisposed.

Relationship of terminal hair to genital development. In general, it was found that the appearance of pubic hair corresponded roughly with the stage of genital development classified as pubescent, though either might precede or follow the other ; that axillary hair appeared relatively late, i.e. corresponding with the grading of adolescence ; and that hair on the linea alba was very late in appearance, being observed once only in the whole series. Whilst an exact analysis of the order of appearance of primary and secondary sexual characters could only be attempted by serial examinations of the same boys over a period of five or six years, the single examination, particularly of the pubescent boys, yielded certain information.

Of the boys classified as pubescent, 52 per cent. showed pubic hair (P1 to P3) and pubescent genital development, but no axillary hair ; 12 per cent. showed the same signs plus axillary hair (A1 or A2); 10 per cent. showed pubic hair with genitalia graded as prepubescent; and 23 per cent. showed pubescent genitalia with absence of both pubic and axillary hair. In two cases, moderately profuse axillary hair was present in the absence of pubic hair, and with genitalia showing only the earliest signs of pubescence.

The adolescent group was almost evenly divided between those in which axillary hair was present and those in which it was absent. In all cases pubic hair was present, though this varied from P2 to P5. In

TABLE 4

MEAN INCREASE IN HEIGHT, LEG-LENGTH, AND WEIGHT OF PREPUBESCENT AND PUBESCENT BOYS AGED 13 TO 14 YEARS (SCHOOL A) OVER A PERIOD OF 100 DAYS

	Increased height (cm.)			Increased leg-length (cm.)			Increased weight (g.)		
	Mean	Standard error	Standard deviation	Mean	Standard error	Standard deviation	Mean	Standard error	Standard deviation
Prepubescent	1·51	0·15	0·579	1·23	0·26	1·045	439·43	138·91	552·83
Pubescent	2·10	0·19	0·910	1·32	0·23	1·105	1,202·89	178·96	853·62

three cases, the growth of axillary hair appeared more advanced than that of pubic hair.

No relationship could be demonstrated between the occurrence of gynaecomastia and the presence of axillary hair.

Skin changes. It is generally recognized that the occurrence of comedones, acne, and possibly follicular keratosis are, or may be, related to the action of androgenic hormones. As already indicated, acne was seen in only a very small percentage of cases, whilst follicular keratosis appeared too variable in relation to season and exposure to be accurately correlated with puberty.

Comedones occurring on the facial area were, however, noted in 19·7 per cent. of the prepubescent group, 41·0 per cent. of the pubescent group, and 76·2 per cent. of the adolescent group.

Discussion

Whilst accurate maturity-grading of boys should include not only clinical examination but also radiological assessment of ossification and estimation of hormone-excretion, the present study indicates that grading on clinical grounds alone may serve to bring out certain differences in mean height and weight between the groups studied; and that such differences are present long before puberty is reached. If, as seems probable, there are also changes in rate of growth peculiar to the onset and duration of puberty, it follows that standard height and weight curves compiled without reference to the stage of maturity of the children measured will be deceptive when compared with the growth curves of an individual child; thus although the 13- to 14-year-old group contained the greatest number of pubescent boys, it was clear that the age of onset of puberty varied considerably in different subjects, and that in standard curves based on chronological age only, ' puberty-growth ' will not be as clearly demonstrable at any one age-period as it may be in the individual. The relationship of puberty to increase in weight has also a practical importance when mean weight curves are used in the assessment of nutrition of communities of children in their teens, and it has previously been suggested (Ellis, 1945) that severe malnutrition may itself be responsible for a general delay in the onset of puberty, reflected in the shape of the mean weight curve of the affected groups.

Since the present study is concerned only with boys up to the age of sixteen, it gives no information with regard to the mean adult height and weight of those who mature early as compared with those who mature late. Studies made on girls and on adult women, in whom the age of onset of menstruation was known, indicated that the pyknic type tends to mature earlier (Pryor, 1936) and that the adult height of those who menstruated late tends to be greater than that of girls in whom the menarche occurs early. In order to obtain comparable information in the case of adult males, it would be necessary to follow up boys who had been examined and graded during their teens, since the age of onset of puberty is seldom accurately remembered or noted in their school medical records. However, if clinical assessment of maturity were included in the routine medical examination of boys, it would be possible to see whether adult height and weight showed any significant correlation with early or late maturity in the male. Whilst improvement on the clinical criteria employed in the present study could no doubt be made, it is suggested that they provide a simple, if rough, guide to maturity-grading which would serve this purpose.

Another possible application of maturity-grading is in relation to education and physical performance. Since education is based very largely on grouping by chronological age, it follows that most classes during the early and middle teens will contain boys varying from physically immature children to those who are well advanced in adolescence. Whilst intellectual development is obviously not commensurate with physical development, there are certain disadvantages in educating together boys of very different physical, and often emotional, stages of maturity. When large numbers have to be catered for, and classes have in any case to be subdivided on other than strictly intellectual grounds, it has been suggested that maturity-grading might be used as a basis of division, boys of roughly the same maturity then being educated together. With regard to physical performance, a natural division into maturity plus individual aptitude is more likely to establish itself automatically in athletics and organized games, but in the case of boys in employment, the burden may fall very unequally on the mature and the immature. Legislation with regard to juvenile employment of boys is entirely based on age, whereas in fact maturity is a better basis for deciding the physical demands that can be made on the individual. The raising of the school leaving-age to fifteen will have, amongst other advantages, the result that the proportion of prepubescent boys entering employment will be substantially reduced.

Whilst clinical maturity-grading applied to groups allows certain generalizations with regard to mean height and weight, it should, however, be emphasized that anthropometric measurements alone are an ureliable guide in the prediction of onset and duration of puberty in the individual. (Thus Flory (1935) in the case of girls found that anthropometric measurements were much inferior to radiological assessment of maturity in predicting the onset of menstruation.) It cannot be assumed that an individual child who is below the mean height and weight for his age will necessarily mature late rather than early. Similarly the rapidity with which individuals pass from one maturity-grade to the next is likely to vary considerably, and it follows that any application of maturity grading to educational grouping or employment can have only a limited and temporary value. The following example (not included in the present series) is quoted in detail, as it illustrates the early maturation of a small child and also the extremely rapid increase in height and weight which may take place at puberty.

M. J. was born prematurely at seven months, weighing 3½ lb. (1·59 kg.). At two months he weighed 6 lb. (2·73 kg.), at one year 19 lb. (8·6 kg.),

at two years 24 lb. (10·9 kg.), and at four years 33 lb. 7 oz. (15·2 kg.). He was examined at the age of eleven years five months, when he was graded as prepubescent ; he then weighed 68 lb. (30·9 kg.) and measured 4 ft. 6 in. (137·2 cm.) in height. At twelve years two months he showed the presence of pubic hair (P2) and early genital development, and was graded as pubescent. At twelve years five months he had reached ' established adolescence ' ; the voice was broken, pubic hair was profuse, axillary hair was present, and the ' adolescent moustache ' was appearing on the upper lip. His height was 5 ft. 1½ in. (156·2 cm.) and weight 105½ lb. (48·0 kg.). He had, therefore, not only matured early (receiving a higher maturity-grading at twelve years five months than any of the boys in the 12- to 13-year-old group), but had passed from prepuberty to adolescence in the space of one year, during which time he had increased 7½ in. (19 cm.) in height and 37½ lb. (17 kg.) in weight. Apart from vasovagal attacks, coincident with the onset of puberty, he appeared healthy, and no pathological cause for his rapid growth and development was found.

Summary and Conclusions

1. Two hundred and eight boys, aged eleven to sixteen years, from two residential schools, were graded on a basis of clinical assessment into three maturity-groups viz. prepubescent, pubescent, and adolescent. Comparison was made between the mean heights and weights of boys from the same school who fell into the same yearly age-groups but into different maturity-groups.

2. It was found that not only were boys of the higher maturity-group heavier and taller than their contemporaries in the lower maturity-group, but that differences between the growth curves could be demonstrated as far back as the sixth year (in the case of boys from School A, where records were available to this time).

3. The growth curves suggested that there was an increased annual gain in weight, and to a lesser extent in height, which could be related to the onset and duration of puberty.

4. This was confirmed by the re-examination of one age-group after a period of one hundred days, when it was found that increase in height and weight of pubescent boys was significantly greater than that of prepubescent boys in the same school.

5. Gynaecomastia was observed in none of the prepubescent group ; in 12·9 per cent. of the pubescent group ; and in 32·1 per cent. of the adolescent group.

6. Observations were made on the relationship of certain primary and secondary sexual characters during puberty.

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References

Catchpole, H. R., Greulich, W. W., and Sollenberger, R. T. (1938). *Amer. J. Physiol.*, **123**, 32.

Ellis, R. W. B. (1945). *Arch. Dis. Childh.*, **20**, 97.

Flory, C. D. (1935). *Child Development*, **6**, 1.

Godin, P. (1934). Quoted by Laroche, G. (1938). *La Puberté*. Paris.

Greulich, W. W., Doriman, R. I., Catchpole, H. R., Solomon, C. I., and Culotta, C. S. (1942). *Somatic and Endocrine Studies of Puberal and Adolescent Boys*. Nat. Res. Council, Washington.

Nathanson, I. T., Towne, L. E., and Aub, J. C. (1939). *Endocrinol.*, **24**, 335.

—— —— —— (1941). *Ibid.*, **28**, 851.

Pryor, H. B. (1936). *J. Pediat.*, **8**, 52.

Stone, C. P. and Barker, R. G. (1937). *Human Biol.*, **9**, 1.

Talbot, N. B. Butler, A. M., Berman, R. A., Rodriguez, P. M., and MacLechann, E. A. (1943). *Amer. J. Dis. Child.*, **65**, 364.

Weber, F. P. (1946). *Rare Diseases and some Debatable Subjects*. London.

SOME OBSERVATIONS ON THE GROWTH OF CHILDREN

BY

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The factors influencing the health and growth of the child during the first five years of life are still only partly understood. The School Medical Service has expanded considerably since it was first begun in 1907, and side by side with it has grown up a health organization for the care of mothers and infants. These services were at first largely concerned with the detection and correction of defects, but latterly researches on nutrition and other aspects of child hygiene have given a new significance to their work, and preventive or constructive medicine has been increasingly emphasized. The care of the child in the years between infancy and school age has, however, received little attention up till now, and the healthy child in this formative period can scarcely be said to have been studied in detail. One reason for this is that the majority of children in this age group do not remain under close and continuous medical supervision unless they are ill or crippled, so that doctors have small opportunity for consecutive studies of unimpaired growth and development.

Physical and other characteristics are determined in part by heredity, in part by maternal health and efficiency, and in part by nutrition and environment. The relative importance of each of these factors in the early years is difficult to assess, and there are few accepted standards of comparison available for children between birth and five years old. Here, as with adults, medicine has tended to base too many of its 'normal' standards on observations made on patients.

Data. The following study was undertaken with a view to assessing physical development at the several ages in respect of the more important dimensions in children up to five years of age, and to show by means of averages the natural rates of growth of trunk and limbs. Such a scheme must necessarily entail observations on a large number of children, and the wartime day nurseries offered an opportunity for examinations of healthy children in the required age group, while entailing the minimum of interference with their normal routine, and of inconvenience to the parents. The investigation was preliminary to a more detailed continuous study of health, growth, and sickness in the preschool child in all social groups and starting from the first weeks of life, and it provided experience in the technique of the measurements that are now being employed in the major survey.

The investigation was based on 465 children between the ages of a few weeks and five years, who were resident in the day nurseries of the City of Oxford during the period January to March, 1944. The number of infants at 0–6 months and at 6–12 months was much too small for adequate statistical analyses and thus, in the subsequent tables, only the average measurements for these two groups are recorded. The period under 12 months was divided into these two component parts because other investigators have asserted that there is a spurt in growth in the latter part of the first year of life.

Some measure of social selection was inevitable. For the most part, the parents of the children were representative of the Registrar-General's Social Class (according to occupation) III. In this Class, and in Classes II and IV, general standards are probably higher in Oxford than in a mainly industrial city. Nutritional advantages have been uniformly improved during the war period by the special provisions for mothers and infants.

Methods. Among the children examined, four (0·84 per cent.) were found on clinical examination to show a marked abnormality. There was one case of congenital spastic diplegia; one child with rickets; one mentally defective child; and one undernourished 'behaviour problem' child. These children were excluded from the tables. Two children had a previous history of conditions satisfactorily treated: one case of bilateral congenital dislocation of the hips, and one case of 'heart trouble.' Neither showed any abnormal physical sign. These children are included in the tables.

Franzen (1929) has shown that measurements of the weight and height alone are not satisfactory for nutritional assessment. The skeletal dimensions, especially the chest and hip measurements, are of importance, and, to a lesser degree, the development of the muscular and subcutaneous tissues. Franzen and Palmer (1934) recommend measurements of arm girth, chest depth, and width of pelvis as suitable for nutritional assessment. Their measurements were made in conjunction with a clinical examination on schoolchildren over six years old, and normal tables of reference were constructed. By means of these the undernourished children could be detected with more certainty and agreement than on clinical grounds alone.

In taking measurements such as these observers made, much depends on the co-operation of the child, which, after school age is attained, is reasonably good. Under five years old, however, co-operation of the child is a very variable factor. In the present study it was found necessary to select measurements which could be made with ease and quickness without tiring or boring the child, and

which would indicate the skeletal dimensions and the development of the muscular and subcutaneous tissues at the various ages. Chest and arm measurements were found to be too difficult to make with any accuracy in young children. After a good deal of experiment, the following observations, and a clinical examination of the child, were made in each case:

Weight.
Crown-rump length, or ' sitting height.'
Length of lower limb.
Circumference of calf.
Circumference of head.
Antero-posterior and transverse diameters of the head.
Width of pelvis.

All measurements were made by one observer, and accuracy was checked by repeating measurements on the same child at various sessions.

WEIGHT. The machines were checked each time before use, and the children were weighed clothed only in a vest.

CROWN-RUMP LENGTH. This measurement was taken with the child lying supine and straight on a flat table, with the crown of the head against a smooth, flat surface, perpendicular to the table. The child's hips were flexed to a right angle by an assistant, who supported the legs with the knees bent to keep the pelvis flat on the table. A T-square was placed across the table against the child's buttocks, and the distance in centimetres from the crown of the head to the buttocks was taken.

LENGTH OF LOWER LIMB. This measurement was taken with a steel tape measure. The upper end of the great trochanter was palpated, and the distance in centimetres from this point to the tip of the external malleolus, down the lateral side of the leg, was measured.

CIRCUMFERENCE OF THE CALF. This measurement was taken with a flexible steel tape-measure over the belly of the gastrocnemius. The leg was measured from the head of the fibula to the external malleolus, and the junction of the upper one-third and lower two-thirds of the leg was marked. At this point the circumference of the calf was taken with the legs relaxed, and the feet in the position of rest. The tape measure was pulled tight so that its surface lay flush with the skin, but without indenting the subcutaneous tissues.

CIRCUMFERENCE OF THE HEAD. The tape-measure was passed round the head over the parietal and occipital eminences.

ANTERO-POSTERIOR AND TRANSVERSE DIAMETERS OF THE HEAD. These measurements were taken with a pair of steel callipers: the first from the glabella to the most prominent part of the occipital tuberosity; and the second between the most prominent parts of the parietal eminences.

WIDTH OF PELVIS. The intercristal diameter was taken with the child lying supine. Callipers were applied on the outer edge and at the widest part of the iliac crests.

Results of measurements. Tables 1A and 1B give the mean values of the somatometric observations according to age and sex. As is to be expected, the mean value for each variable increases with age, but not in a uniform manner. The table would appear to indicate that in the latter part of the first year of life there is a spurt in growth in each variable, the magnitude of which can be more accurately indicated by the percentage than by the difference between the absolute values; but it must be stressed that the numbers examined in this age-group were too small to permit of any dogmatism. The percentage increase in successive age periods is shown in table 2.

There is a general indication thatthe rate of increase drops with age more regularly for some measurements than for others. This is particularly true of sitting height. In the first half year its increase is 11·89 per cent. for males, and 12·85 per cent. for females; at approximately 2 years the ratios are 7·44 per cent. and 9·00 per cent. respectively; in the final age-group the rate of increase for males and females drops to 4·40 per cent. and 4·96 per cent.

A comparison of tables 1A and 1B, summarized in table 3, shows the difference between the sexes at each age period.

In most instances the mean values for all measurements in all age-groups are greater among the males than among the females, with the exception of the period 6–12 months, when in six out of the eight variables considered (the weight, all three head measurements, the width of the pelvis, and the circumference of the calf), the female value is the

TABLE 1A.—MALES
AVERAGE MEASUREMENTS ACCORDING TO AGE

Measurement, cm.	0–6 months	6–12 months	1–2 years	2–3 years	3–4 years	4–5 years
Sitting height	42·40	47·44	51·76±0·28	55·61±0·30	59·35±0·35	61·96±0·06
Head—circumference ..	40·76	44·87	48·30±0·35	49·86±0·19	50·79±0·23	51·18±0·17
Head—transverse diameter	11·02	12·47	13·39±0·08	13·72±0·07	13·97±0·06	14·12±0·01
Head—antero-posterior..	13·96	15·23	15·93±0·13	16·71±0·10	17·12±0·09	17·33±0·08
Calf	14·74	16·89	18·92±0·20	19·86±0·15	20·66±0·52	21·49±0·22
Pelvis	11·12	11·97	13·81±0·15	15·29±0·11	16·55±0·07	17·46±0·11
Leg	22·30	25·85	31·58±0·48	36·75±0·38	41·87±0·34	45·91±0·24
Total number examined..	5	15	39	56	59	58
Weight, lb.	13·50	18·37	25·12±0·42	30·04±0·47	34·59±0·44	38·46±0·55
Total number examined..	5	14	39	50	56	57

TABLE 1B.—FEMALES
AVERAGE MEASUREMENTS ACCORDING TO AGE

Measurement, cm.	0–6 months	6–12 months	1–2 years	2–3 years	3–4 years	4–5 years
Sitting height	40·86	46·11	50·89±0·36	55·47±0·34	58·84±0·32	61·76±0·48
Head—circumference	39·64	45·00	46·98±0·22	48·83±0·18	49·64±0·18	50·24±0·86
Head—transverse diameter	10·89	12·75	13·04±0·08	13·57±0·10	13·71±0·07	13·73±0·07
Head—antero-posterior	13·47	15·25	15·73±0·09	16·40±0·11	16·66±0·10	16·90±0·10
Calf	14·13	17·66	18·36±0·19	20·18±0·21	20·86±0·37	21·82±0·21
Pelvis	10·18	12·36	13·55±0·58	15·17±0·13	16·19±0·12	17·36±0·13
Leg	21·61	25·36	32·09±0·41	38·26±0·93	42·08±0·33	45·92±0·36
Total number examined	9	11	35	49	71	54
Weight, lb.	12·25	19·58	23·79±0·47	29·66±0·56	34·38±0·49	38·50±0·82
Total number examined	8	11	33	42	65	51

TABLE 2
PERCENTAGE INCREASE IN GROWTH AT SUCCESSIVE AGES

	Sex	6–12/0–6 months	1–2/½–1 years	2–3/1–2 years	3–4/2–3 years	4–5/3–4 years
Sitting height	M	11·89	9·11	7·44	6·73	4·40
	F	12·85	10·37	9·00	6·08	4·96
Head—circumference	M	10·08	7·64	3·32	1·87	0·77
	F	13·52	4·40	3·94	1·66	1·21
Head—transverse diameter	M	13·16	7·38	2·46	1·82	1·07
	F	17·08	2·27	4·06	1·03	0·15
Head—antero-posterior diameter	M	9·10	4·60	4·90	2·45	1·23
	F	13·05	3·15	4·26	1·59	1·44
Calf	M	14·59	12·02	4·97	4·03	4·02
	F	24·98	3·96	9·91	3·36	4·60
Pelvis	M	7·64	15·37	10·72	8·24	5·50
	F	21·41	9·62	11·95	6·72	7·23
Leg	M	15·92	22·17	16·37	13·93	9·65
	F	17·35	26·54	19·23	9·98	9·13
Weight	M	36·07	36·74	19·59	15·15	11·19
	F	59·84	21·50	24·67	15·91	11·98

TABLE 3
DIFFERENCES BETWEEN THE AVERAGE MEASUREMENTS OF MALES AND FEMALES ACCORDING TO AGE

		0–6 months	6–12 months	1–2 years	2–3 years	3–4 years	4–5 years
Sitting height	M-F	+1·54	+1·33	+0·87±0·46	+0·14±0·45	+0·51±0·47	+0·20±0·48
Head—circumference	M-F	+1·12	−0·13	+1·32±0·41*	+1·03±0·26*	+1·15±0·29*	+0·94±0·88
Head—transverse diameter	M-F	+0·13	−0·28	+0·35±0·11	+0·15±0·12	+0·26±0·09*	+0·39±0·07*
Head—antero-posterior	M-F	+0·47	−0·02	+0·20±0·16	+0·31±0·15	+0·46±0·13*	+0·43±0·13*
Calf	M-F	+0·61	−0·77	+0·56±0·28*	−0·32±0·26	−0·20±0·64	−0·33±0·30
Pelvis	M-F	+0·94	−0·39	+0·26±0·60	+0·12±0·17	+0·36±0·14*	+0·10±0·17
Leg	M-F	+0·69	+0·49	−0·51±0·63	−1·50±1·00	−0·21±0·47	−0·01±0·43
Weight	M-F	+1·25	−1·20	+1·33±0·63*	+0·38±0·73	+0·21±0·65	−0·04±0·99

* The values marked with an asterisk are significantly different.

greater. This advantage is maintained only in the length of the lower limb after the first twelve months.

Baldwin (1921) made an extensive study of growth in children up to adolescence. He found that the greatest increase in length took place in the first year of life, and that, on the average, in the pre-school period, boys were heavier and longer than girls. Meredith and Boynton (1937) agree with these findings, and also show that, in measurements of the limbs, males have the advantage over females. They found that in both sexes the annual percentage increase in growth was greatest in the first, third, and sixth years. Hill and Magee (1938) studied the increase in weight and length in infants during the first year of life, and concluded that the

TABLE 4

CORRELATION COEFFICIENTS BETWEEN VARIOUS MEASUREMENTS

Age	Sex	No.	Head diam. a.-p. and trans.	No.	Sitting height and length of leg	No.	Sitting height and weight	No.	Sitting height and width of pelvis	No.	Weight and width of pelvis
1–2	M	39	+0·511±0·162	39	+0·361±0·162	39	+0·658±0·162	39	+0·603±0·162	39	+0·725±0·162
	F	35	+0·439±0·172	35	+0·690±0·172	34	+0·543±0·174	34	+0·598±0·174	34	+0·884±0·174
2–3	M	56	+0·191±0·135	55	+0·597±0·136	50	+0·671±0·143	56	+0·466±0·135	50	+0·674±0·143
	F	49	+0·288±0·144	49	+0·644±0·144	42	+0·701±0·156	49	+0·410±0·144	42	+0·652±0·156
3–4	M	59	+0·171±0·131	59	+0·590±0·131	56	+0·581±0·135	59	+0·578±0·131	56	+0·711±0·135
	F	71	+0·255±0·120	71	+0·508±0·120	66	+0·685±0·124	71	+0·264±0·120	66	+0·496±0·124
4–5	M	58	+0·268±0·133	58	+0·494±0·133	57	+0·525±0·134	58	+0·563±0·133	57	+0·249±0·134
	F	54	+0·311±0·137	54	+0·776±0·137	51	+0·775±0·141	54	+0·641±0·137	50	+0·347±0·143

absolute and relative gains in weight drop with length and age; males are 6 per cent. to 9 per cent. heavier and 2 per cent. to 3 per cent. longer than females; and the greatest increase in length takes place at 9–10 months old. None of these authors found any significant difference in growth between the sexes during the pre-school period.

Correlation between variables. It is generally recognized that there is a fair degree of correlation between the dimensions of somatometric variables in adults, but the extent of such a relationship in children under five has not been extensively studied. It was, therefore, desirable to ascertain the correlations between some of the variables in this age period. The results are given in table 4, which shows the correlations between: (a) antero-posterior and transverse diameters of the head; (b) sitting height and length of lower limb; sitting height and weight; sitting height and width of pelvis; and (c) weight and width of pelvis.

As is to be expected, the correlations are all positive in sign, but vary in size at the various ages. There is little evidence of a definite correlation between the antero-posterior and transverse diameters of the head in either sex, except at 1–2 years, when the correlations are significant for both males (+0·511±0·162) and females (+0·439±0·172). The association between sitting height and weight is the most consistent, as in both sexes the coefficients are greater than 0·5, and in females of 4–5 years the value is as high as +0·775±0·141. The correlation of pelvic measurements with both sitting height and weight is of interest. For children under 4 years, the pelvic measurement is more closely related to weight than to sitting height, but above this age the reverse is apparent. The correlation between weight and the width of the pelvis declines with increasing age, with one exception. This is among males of 3–4 years, where the correlation is +0·711±0·135. Among females the correlation falls from +0·884±0·174 at 1–2 years, to +0·347±0·143 at 4–5 years. No other pair of associated variables shows this decline with increasing age. Although there is a fairly high positive correlation between each pair of variables (weight, sitting height, and width of pelvis), it is impossible to be certain that the size of the crude coefficient represents the true relation between them, as physical characteristics are interrelated. Before the basic connexion between any pair can be shown, it is necessary to eliminate the influence of other variables in the relationship. For example, weight and width of pelvis are highly correlated; but each of these is also correlated with sitting height. What, then, is the relation between weight and width of pelvis, when the sitting height is held constant? This can be discovered by means of partial correlation coefficients, which are shown in table 5, together with the Z transformation and its significance.

The table shows the important relationship between weight and width of pelvis in children 1–4 years old. Here the values are highly significant,

TABLE 5

PARTIAL CORRELATION COEFFICIENTS BETWEEN VARIOUS MEASUREMENTS

Age	Sex	Partial correlations	Z	Standard Error
1–2	M	r13·2=0·2434	0·248	±0·169
		r23·1=0·5466	0·614	±0·169
	F	r13·2=0·2995	0·309	±0·182
		r23·1=0·8291	1·185	±0·182
2–3	M	r13·2=0·0251	0·250	±0·147
		r23·1=0·5507	0·619	±0·147
	F	r13·2=−0·0870	−0·087	±0·162
		r23·1=0·5604	0·634	±0·162
3–4	M	r13·2=0·2886	0·297	±0·139
		r23·1=0·5634	0·638	±0·139
	F	r13·2=−0·1198	−0·120	±0·127
		r23·1=0·4485	0·483	±0·127
4–5	M	r13·2=0·5244	0·738	±0·137
		r23·1=−0·0662	−0·066	±0·137
	F	r13·2=0·6278	0·738	±0·146
		r23·1=−0·3090	−0·319	±0·146

1—Sitting height.
2—Weight.
3—Width of pelvis.

whereas the values of Z for sitting height and size of pelvis are less than twice their standard errors. In children of 4–5 years the reverse is true. Weight in relation to width of pelvis is less important than the association between sitting height and width of pelvis.

Summary and Conclusions

Although the data relating to infants under one year in this investigation are few in number, they would appear to suggest that the greatest period of growth occurs in the latter half of the first year of life.

Up to 5 years old growth in the male is, on the whole, greater—but not significantly greater—than in the female.

The highest degree of relationship among the variables observed is found between sitting height and weight. Up to 4 years the width of the pelvis is more closely correlated with the weight than with the sitting height, but this alters with age, so that at 4–5 years the width of the pelvis is more closely related to the sitting height.

It is a pleasure to record my thanks to Dr. G. C. Williams, Medical Officer of Health, Oxford, for the facilities which made this enquiry possible; to Dr. Archer, Assistant Medical Officer of Health, for permission to make observations in the day nurseries; and to the staff of the nurseries for their willing co-operation. I am also indebted to Dr. W. T. Russell for statistical assistance, and to Professor J. A. Ryle for advice and criticism.

References

Baldwin, B. T. (1921). *Univ. Iowa Studies in Child Welfare*, **1**, 1.

Franzen, R. (1929). *Amer. Child Hlth. Ass. Publ. Schl. Hlth. Mon.*, No. 2.

——, and Palmer, A. (1934). *Ibid.*, **12**, 138.

Hill, A. B., and Magee, H. E. (1938). *Med. Off.*, **60**, 157.

Meredith, H. V., and Boynton, B. (1937). *Hum. Biol.*, **9**, 366.

THE BLOOD IN INFANCY

BY

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(From the Radcliffe Infirmary, Oxford)

Introduction

In view of the vast amount of work which has been done on the study of the blood picture in the infant and young child, it might seem superfluous to add to the number of communications. The story has already been told by so many workers, and with such apparent unanimity on the general features, that there would seem little reason to doubt the main conclusions. However, it is always worth while reviewing afresh even a question considered settled, if it can be done from a new angle. If this is possible, additional light may be shed on some aspect of the problem so that a different, and perhaps a more correct, conception of the processes at work is obtained. It is because of this that I consider some observations which I have been making during the past two or three years are worthy of publication.

In the past, for example, conclusions regarding the formation and destruction of blood have been drawn for the most part from a consideration of the percentage concentration of the haemoglobin and red corpuscles in the circulating blood. Such a method does not reveal the total amount of haemoglobin or number of red blood cells in the body, which knowledge is essential for a correct estimate of haemopoiesis. It must be admitted, of course, that in the case of a constituent of the body like blood, which normally bears a definite relationship to body weight, the percentage concentration of its constituents may permit of fairly reliable conclusions in an individual of constant weight, as, e.g. the full-grown adult. Nevertheless, it has long been appreciated that rapid variations in body weight, both in the adult and in the child, either in consequence of dehydration or oedema, give rise to anomalous readings and thus to false conclusions; but so far as I am aware, the variations in weight of the normally growing child have never been taken into consideration. It is true that the variations in weight during the process of natural growth of the infant are not so rapid as they are during the development of oedema after renal disease, or of dehydration from an acute enteritis. The variations in weight from growth, however, are considerable, especially during the early months of life. During the first six months the average child doubles its weight, and, therefore, should double its quota of blood.

That there is a want of correlation between body growth and blood formation in the early weeks of life is suggested from the fall in the concentration of the haemoglobin and red cells, but from observations on the concentration of haemoglobin and red cells alone it is impossible to say whether this is due to a lag in blood formation, or to an increased rate of destruction of blood, any more than that the variations in haemoglobin and red cell concentrations in the presence of dehydration or oedema point to abnormalities in the processes of formation and destruction of blood. The correct answer to what is happening can only be obtained from a knowledge of the nature of the change, if any, in the total amount of blood (haemoglobin and red cells). The importance of this conception was first pointed out to me by Dr. Robb-Smith, who suggested that it would be interesting to see how the absolute amount of haemoglobin and total number of red cells in the circulating blood behaved during the neonatal period, for in this way the key to the solution of the much discussed problem of excessive haemolysis might be obtained.

Material. Since 1941, through the kind co-operation of Prof. Chassar Moir, I have had the opportunity of studying the blood picture in the newborn in his Department at the Radcliffe Infirmary, Oxford, and of following the course of events in these children throughout their first year of life. In addition, I have collected isolated observations in a large number of infants under my own care in the Children's Department of the same hospital. To Dr. R. G. Macfarlane I am indebted for much advice and for most of the blood examinations, which were carried out by his technicians. This help was so arranged that, as a rule, the blood examinations were performed by one individual so that some general constancy in standards was maintained.

The blood in the foetus was obtained from the umbilical cord immediately after delivery and before pulsation had ceased. In the newborn infant blood was obtained either by heel puncture or from a scalp vein. There tends to be a slightly greater concentration of haemoglobin and of red cells in the capillary blood as obtained by heel puncture, but the differences are so slight (fig. 1) that it has been deemed justifiable not to differentiate between them and to take either venous blood or capillary blood as representative of the state of matters at any

particular age. In the older infant blood was always obtained by heel puncture, and if this was taken up in heparinized pipettes and collected in heparinized tubes, ample amounts could always be obtained for comprehensive analysis.

The haemoglobin was estimated by Haldane's method, the colour standards employed always

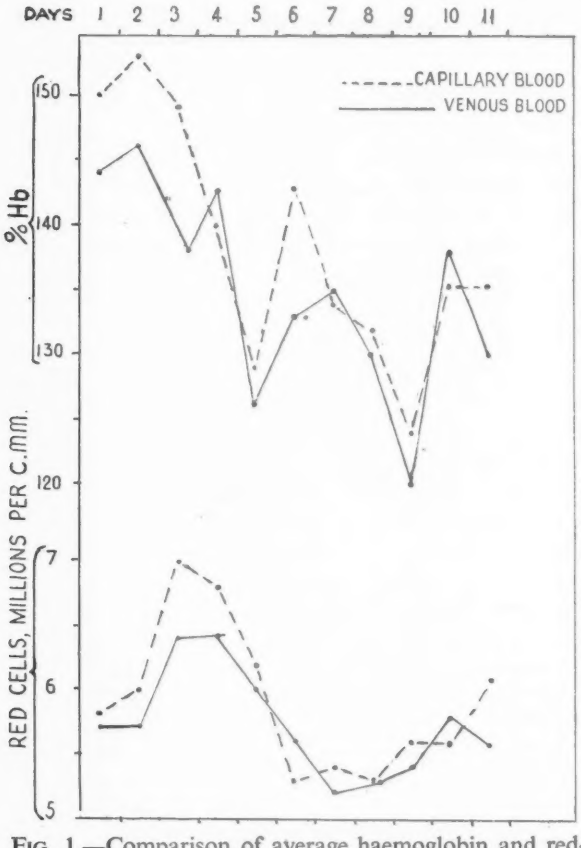

FIG. 1.—Comparison of average haemoglobin and red-cell concentrations in capillary and venous blood in newborn infant.

having been recently tested at the National Physical Laboratory. The reticulocytes were enumerated by the ' wet process.'

Results. Like previous workers, I have found a gradual fall in haemoglobin and red cell concentrations during the early weeks of life. This fall most observers have found to continue till about the age of twelve to fourteen weeks, after which there ensues a slight recovery extending to the end of the first year. Around both of these phenomena, however, there is much controversy. Is the early fall in haemoglobin and red cells due to an abnormal degree of haemolysis, and can the recovery during the later period of infancy be influenced by the administration of additional iron in the diet? These are two of the chief points at issue, and it is to these two problems that our new angle of approach is mainly directed.

Part I: The Neonatal Period

INCREASED HAEMOLYSIS OR DEFICIENT FORMATION? As I have just stated, I was able to corroborate the decline in haemoglobin and red-cell concentrations during the early weeks of life. This phenomenon, if not explicitly declared, is tacitly assumed to indicate an increased rate of destruction with a resultant actual diminution in the amount of blood. Indeed, it is generally assumed that the child is born with more blood than he requires for an independent existence, and so there results immediately after birth an increased destruction of blood (an abnormal degree of haemolysis) to compensate for the altered conditions of post-natal life, viz.: the greater amount of O_2 available from the institution of respiration. It is this increased haemolysis, too, which is fairly generally credited as the reason for the development of jaundice (so-called icterus neonatorum) which attacks the great majority of children during the first week of life.

There are, however, several theoretical considerations which argue against such a sequence of events. In the first place, expansion of the lung is not a sudden event with rapid availability of the alveolar surface. On the contrary, it is a gradual process which requires several weeks for its completion. In the second place, after birth the child is deprived of the extra-medullary haemopoietic tissue on which it was chiefly dependent during foetal life. It would, therefore, seem more logical to advance the hypothesis that the child had an undue need to conserve its red cells, at least until respiration is fully established and medullary haemopoiesis well under way. My own observations support such a contention.

BLOOD QUOTA IN FOETUS. In so far as can be gauged from a study of the percentage concentration of haemoglobin and red cells, there is no support for the idea that the child has relatively more blood during its ante-natal existence than it has during post-natal life. In eleven children of varying degrees of maturity I have compared the haemoglobin and red cell concentrations of foetal blood with those present during post-natal life. The cord blood, withdrawn immediately after delivery and before pulsation had ceased, was taken to represent the state of affairs during foetal life, and after birth the blood was examined at ages varying between two hours and five days. The findings, detailed in table 1, reveal that, without exception, the concentration is increased after birth, the increase within the first few hours of life in both haemoglobin and red cells varying between 13 and 70 per cent., and the haematocrit readings between 10 and 75 per cent. If the conclusion which such a change usually suggests is drawn from these findings, then it seems probable that there is a call for rather more oxygen carriers than for fewer during the critical neonatal period. It would be idle to suggest that such a finding results from an absolute increase in the number of red cells during so short a period of time (as little as five hours) and the explanation of the phenomenon is almost certainly merely an increase in concentration of the blood. Such an increase might result in part from loss of weight due to dehydration which takes place after birth. But that this is the whole explanation is improbable,

TABLE 1

Hb AND RED CELL CONCENTRATIONS AND HAEMATOCRIT READINGS IN CORD BLOOD AND IMMEDIATELY AFTER BIRTH

Name and age	Duration of pregnancy	Haemotocrit reading	Haemoglobin concentration %	Red cell concentration per cu. mm.	Presence of jaundice
				mill.	
R. C.B.	38/52	57	130	4·8	
4½ hrs.			160	6·4	
K. C.B.	37/52	55	120	4·1	
3 days			136	5·4	+
C. C.B.	40/52		110+	3·7	
1½ hrs.			110+	6·6	
2 days			130	5·8	+
A. C.B.	38/52	40	100	3·6	
5 hrs.		70	170	5·8	
4 days			125	5·0	+
J. C.B.	40/52	54	130	4·8	
2 hrs.		68	180	6·1	
10 days		63	140	5·5	+
W. C.B.	41/52	50	114	4·2	
17 hrs.		66	150	5·6	−
R. C.B.	40/52	57	120	4·1	
19 hrs.		75	160	5·9	−
D. C.B.	37/52	44	105	3·0	
4 days		50	100	4·5	−
S. C.B.	35/52	44	104	3·5	
4 days		55			+
S. C.B.	40/52	61	130	4·7	
5 hrs.		66	180	5·2	
5 days			150	6·1	−
W. C.B.	36/52	45	100	4·2	
7 hrs.		60	160	5·7	
S. C.B.	45/52	52	115	5·7	
hrs.		70	175	5·7	
5 days			170	6·1	−

since the increased concentration is much greater than what could occur in this way. For example, the loss of 1 lb., which, by the way, would be an abnormally high figure and in any case would be spread over two or three days, would only account for a change in concentration of some 12 per cent., whereas we have seen that an actual concentration of some 70 per cent. may occur during the first five hours of life. The phenomenon is to me at present inexplicable, but it reveals how dangerous it is to conclude from the red-cell and haemoglobin concentrations during the early hours and days of life, and probably at all ages, what is happening so far as blood formation and blood destruction are concerned.

PERIOD OF MOST RAPID DECLINE IN CONCENTRATION OF BLOOD. In support of the view that there occurs increased haemolysis during the neonatal period, and that this is the cause of icterus neonatorum, it is usually stated that the most rapid decline in the red-cell and haemoglobin concentrations occurs during the earliest days of life (first ten days). This, however, has not been my experience. For the special study of this particular question I have available a set of observations made on almost every day of life during the first two months. The findings in this series are shown in fig. 2. These reveal that the most rapid decline occurs during the second week of life, a point which must have an important bearing on our views regarding icterus of the newborn. During the first week the fall in concentration of red cells amounts to 3·6 per cent., or 0·5 per cent. per day, during the second week to 15 per cent., or 2·0 per cent. per day, i.e. four times as much, and during the period from the third to the eighth weeks inclusive to 4·4 per cent. or, 1 per cent. per day, i.e. only one-fifth of what occurred during the first week and one-twentieth of what occurred during the second week.

In the case of haemoglobin the same general trend is observed but the percentage falls are not identical. During the first week the fall in haemoglobin is almost equal with that of red cells, being 3 per cent. for the seven days or 0·4 per cent. per day, as against 0·5 per cent. per day for the red cells. During the second week, however, the fall in haemoglobin amounts to 23 per cent., or 3·3 per cent. per day, that is, close on 100 per cent. more than in the case of the red cells; and during the period of the third to the eighth weeks inclusive the fall in haemoglobin amounts to 15·3 per cent., or 0·4 per cent. per day, which is 300 per cent. more than that of the red cells.

CHANGE IN SIZE OF RED CELL AFTER BIRTH. This want of harmony in the behaviour of the haemoglobin and red cells might at first sight cast doubt on the reliability of the findings, but it is possible to advance another explanation and one which we think is of special significance. One of the most marked alterations which the blood undergoes in the change-over from foetal to natal life is the diminution in the size of the red cell and, therefore, in the amount of the contained haemoglobin. I regret that I did not make actual measurements of the size of the red cell during this important transition period. I did not at a sufficiently early period in my study appreciate the importance of this factor. However, from the blood counts and haematocrit readings it is possible to form an estimate of the mean corpuscular volume (M.C.V.) and of the mean corpuscular haemoglobin content (M.C.H.), and this I have done in a fairly comprehensive series of infants, in which both cord blood immediately after delivery, and venous and capillary blood at various ages, were examined. The findings are shown graphically in figs. 3, 4, and 5 which supply data for foetus of varying degrees of maturity and for children of varying ages. From these computations it would appear that immediately after birth there results a marked diminution in both the mean corpuscular volume and mean corpuscular haemoglobin content, but no alteration—as is to be

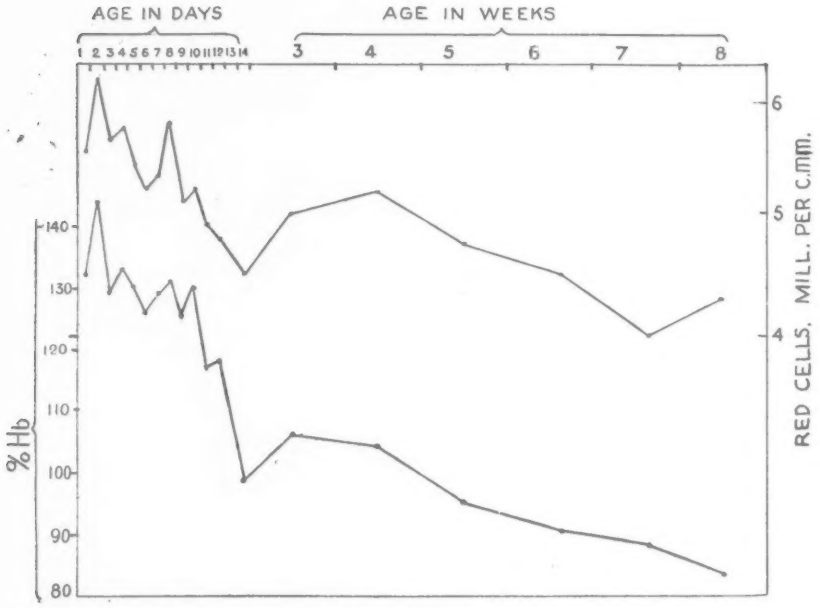

FIG. 2.—Daily average Hb and red cell counts during first four weeks of life.

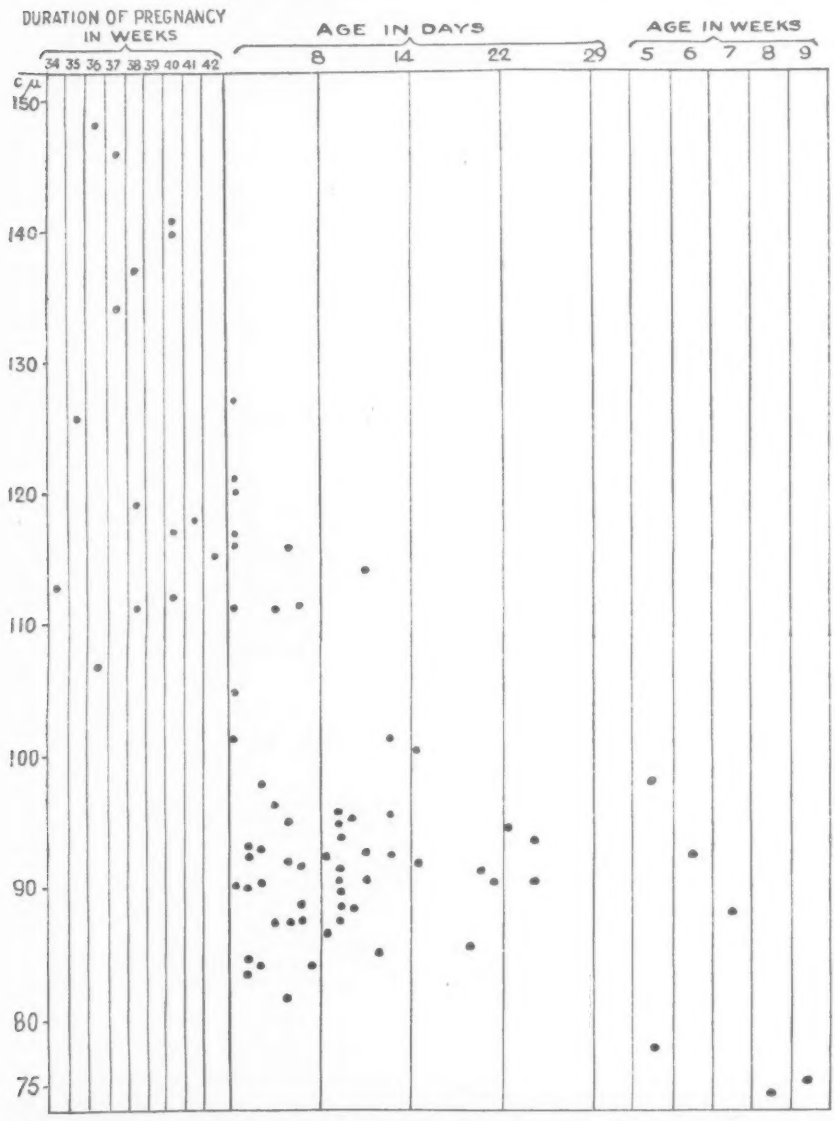

FIG. 3.—Mean corpuscular volume in foetus and newborn child.

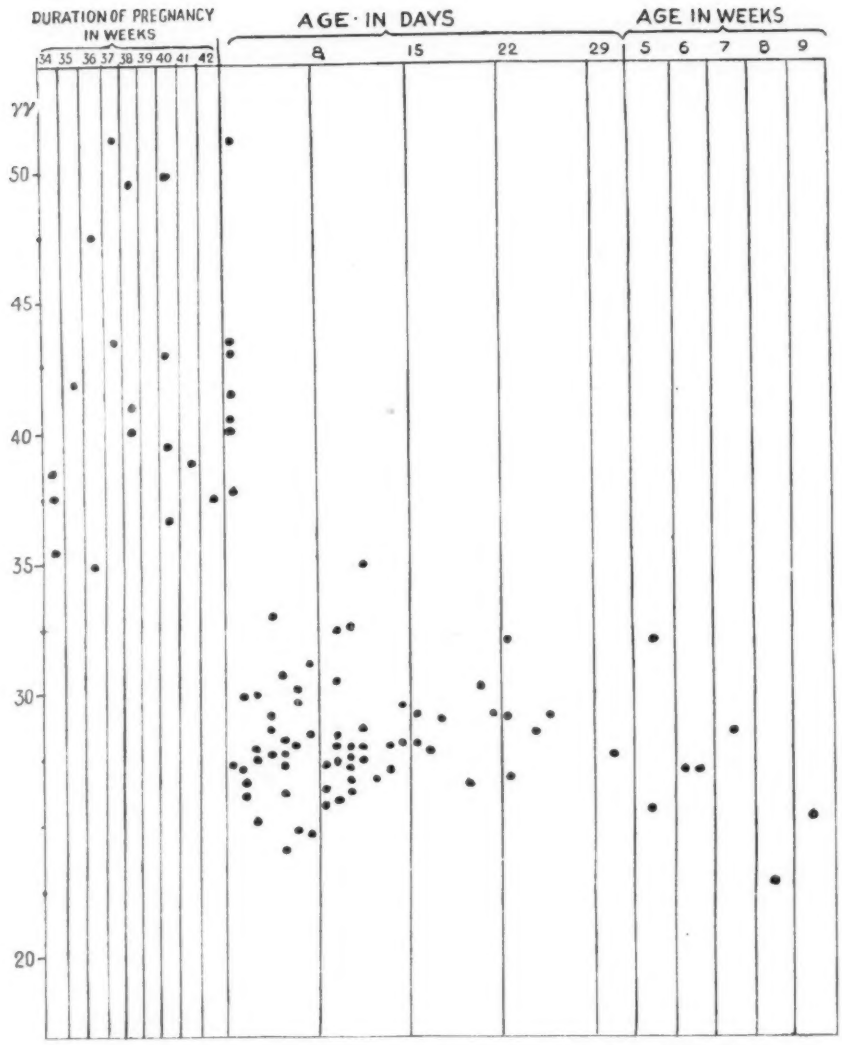

FIG. 4.—Mean corpuscular haemoglobin in foetus and newborn child.

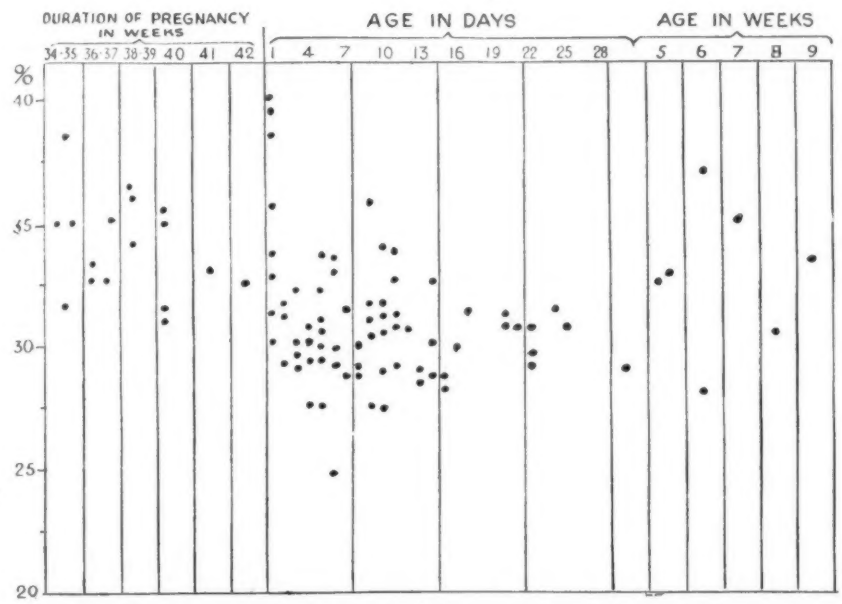

FIG. 5.—Mean corpuscular haemoglobin concentration in foetus and newborn child.

expected—in the mean corpuscular haemoglobin concentration (M.C.H.C.). It will be noted that the maturity of the foetus has little or no influence on the size of the red cell or on its quota of haemoglobin.

It seems to us that it is in this alteration in size of the red cell, and, therefore, in the amount of its contained haemoglobin, that the explanation of the want of harmony in the rates of fall of haemoglobin and red-cell concentrations is to be found. As the foetal red cells are destroyed they are replaced by others of a smaller size but with the same M.C.H.C., so that there is a change in the relationship between red cells and haemoglobin. Moreover, as time progresses, an increasingly greater proportion of the larger foetal cells are replaced by the smaller and more mature cells, so that the alteration in the relationship between the red-cell and haemoglobin concentrations should increase, which, as we have observed, is just what happens. These findings would seem to allow of only one conclusion, viz.: that during this period, whatever the degree of destruction, new blood formation is not inconsiderable. Were it otherwise it is difficult to see how this change in the relative quantities of haemoglobin and red cells could arise.

TOTAL BLOOD HAEMOGLOBIN AND RED CELLS. Although the above observations strongly suggest that there occurs considerable new-blood formation during the neonatal period, no true idea of the extent to which this occurs can be obtained from observations of the haemoglobin and red-cell concentrations alone. In our introductory paragraphs we have already drawn attention to the limitations of such a method of study of the problem, and it was for these reasons that we decided to investigate the variations in the total blood volume during this period.

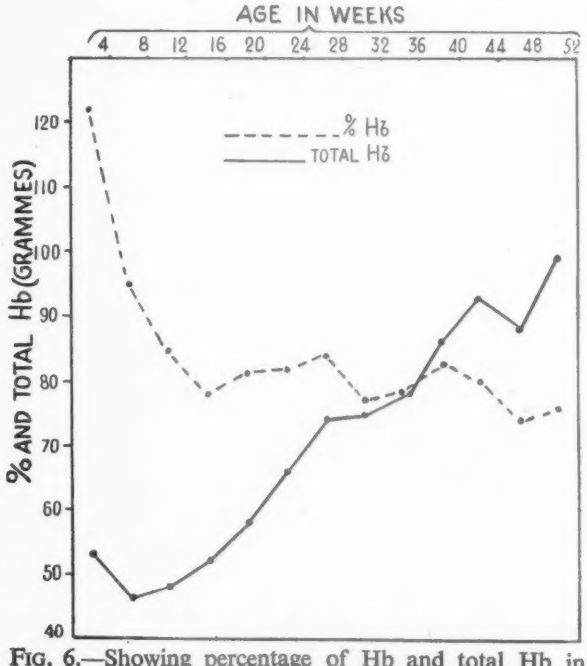

FIG. 6.—Showing percentage of Hb and total Hb in full-time normal infants.

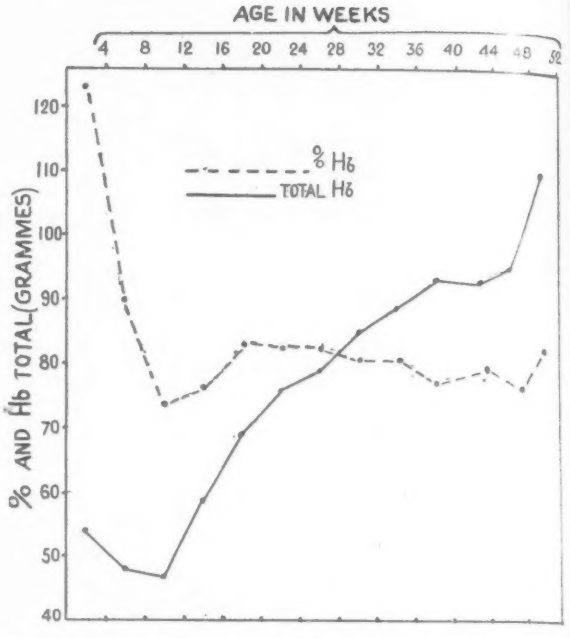

FIG. 7.—Showing Hb percentage and total Hb in normal full-time children receiving additional iron.

We did not find it possible to estimate the blood volume directly. In the foetus and the newborn direct methods are not feasible and so we have been able to make our estimations only indirectly from the weight of the child at the time of the blood examination. We have assumed that for every pound weight there are 40 c.cm. of blood, and, from the blood volume so computed and the haemoglobin percentage (100 per cent. representing 14·8 g. haemoglobin) and red-cell concentration, we have estimated the total blood haemoglobin content in grammes and the red-cell content in millions to the 10^{13} power. The findings are shown graphically in figs. 6, 7, 8, and 9. These graphs show that while there would seem to be an absolute diminution in the amount of blood (expressed in total g. of haemoglobin and millions of red cells) during the early weeks of life, it is neither so marked nor so prolonged as the percentage concentration readings suggest. In all the charts, except in that showing the trend of total haemoglobin in the case of children receiving additional iron, the lowest estimate in total blood is observed during the second month of life, whereas the graphs for percentage concentrations show the lowest readings during the third and fourth months of life. These graphs of total amounts seem to us to reflect a truer perspective in the balance between destruction and formation. We have already remarked on the post-natal disappearance of much of the haematopoietic tissue on which the foetus had depended, and it is, therefore, not surprising that in the early days and weeks of life production lags behind and is not able to compensate for even the normal loss.

RELATION BETWEEN HAEMOLYSIS AND ICTERUS NEONATORUM. Since the fall in the haemoglobin

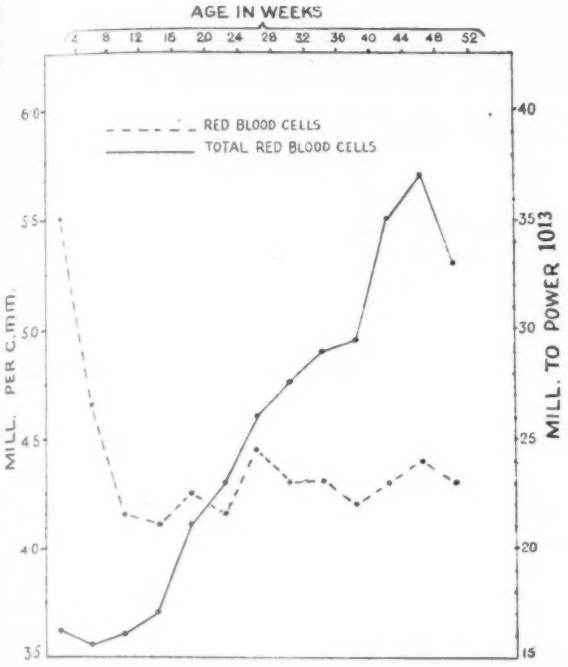

FIG. 8.—Percentage of red blood cells and total red blood cells in normal full-time child.

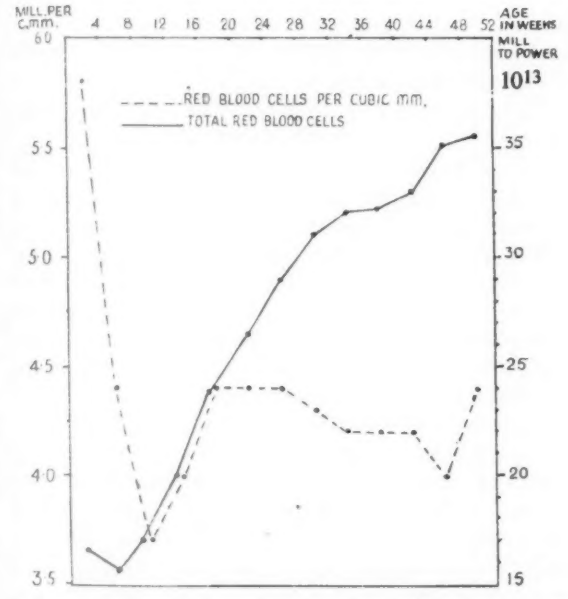

FIG. 9.—Red cells per c.mm. and total red cells in million to power in full-time children receiving additional iron.

and red-cell concentrations is more marked during the second than during the first week of life, it is unlikely that this plays the chief rôle in the production of icterus neonatorum, which usually sets in on the second or third day of life. And the fact that there is little or no difference between the rates of fall in icteric and non-icteric infants renders such an association still less likely (see figs. 10 and 11). The blood in twenty newborn infants, seven of whom developed clinical jaundice, was examined as soon after birth as possible and on every alternate day till due for discharge from hospital, usually the tenth or eleventh day of life. The haemoglobin and red-cell concentrations were determined and the total haemoglobin and red-cell content computed from the weight of the child at the time of the examination.

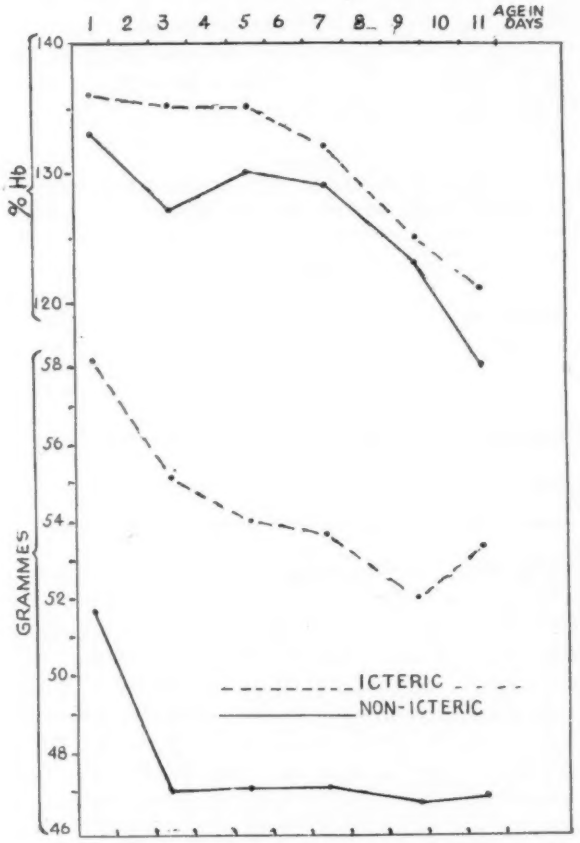

FIG. 10.—Daily haemoglobin percentage and total amount in icteric and non-icteric infants.

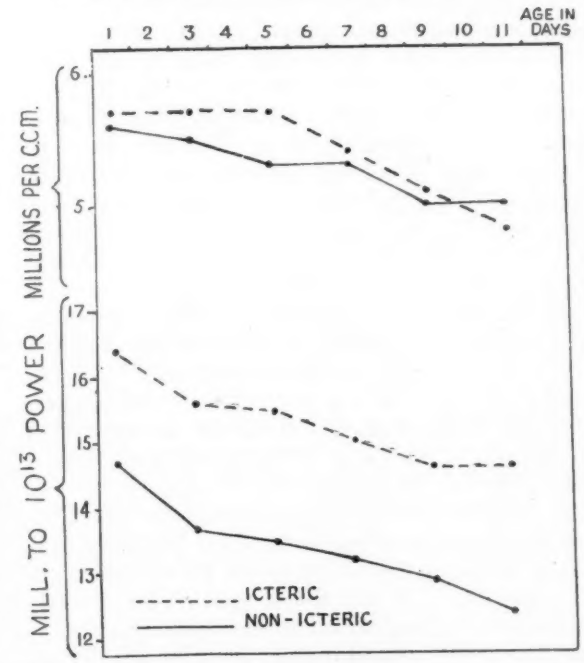

FIG. 11.—Red cells in millions per c.mm., and total amounts in icteric and non-icteric infants.

The means of the findings are shown graphically in figs. 10 and 11. The similarity of the trend of the curves in the two groups—icteric and non-icteric—is striking. During the first seven days the percentage fall in the haemoglobin and red-cell concentrations is identical in both groups of infants, but when we consider the percentage fall in the total amounts of haemoglobin and red cells it is slightly greater in the case of the infants who did not develop jaundice (table 2).

TABLE 2
PERCENTAGE FALL IN Hb AND RED CELLS DURING THE FIRST SEVEN DAYS OF LIFE

Nature of case	No. of cases	Haemoglobin		Red cells	
		% concentration.	Total in g.	mill. per c.mm.	Total mill. 10^{13} power.
Non-icteric	13	3	8·9	5·3	10
Icteric	7	3	7·7	5·3	8·5

FRAGILITY OF RED BLOOD CORPUSCLE TO HYPOTONIC SALINE. In order to find support for the contention that excessive haemolysis occurs during the early days of life, many workers have studied the resistance of the red cell in the newborn to hypotonic saline solutions. On this question, however, there prevails great diversity of opinion. This, I think, is due to the fact that hardly any two observers have employed the same technique and that not one of them has taken into consideration such extrinsic factors as the CO_2 content of the blood and the relative amounts of cells and plasma. It is well known that venous blood is more fragile than arterial blood, with capillary blood occupying an intermediate position. Little wonder, therefore, when venous blood, e.g. from the cord in the foetus or the longitudinal sinus in the newborn, is compared with capillary blood in the older infant, that some workers have concluded that the red cell in the foetus and the newly born is more fragile than during later infancy. And again, the proportion of plasma to cells will influence the final saline content of the mixture, so that tests in which plasma and cells are not controlled by haematocrit readings and reduced to a constant proportion, as recommended by Dacie and Vaughan (1938) are quite unreliable. We have drawn attention to the very different haematocrit readings in foetal blood and that of the newly born so that unless this factor is taken into consideration the results are not comparable.

I (1945) have investigated the resistance of the red cell to hypotonic saline in close on 100 samples of blood, including that of the foetus, the newborn, and the older child. I have found that the blood of the foetus shows a slightly diminished resistance, but in the case of the newborn child the resistance of the red cell is increased, a characteristic which persists for some months. Such a finding suggests that Nature is rather attempting to conserve the red cells, possibly until haemopoiesis is fully established, which, as we have already hinted, would seem necessary during the rapidly developing period of neonatal existence.

PRESENCE OF NUCLEATED RED CELLS AND RETICULOCYTES DURING NEONATAL PERIOD. Moreover, if haemolysis were excessive during the neonatal period, one would expect the usual consequences of such a process, viz., a rise in premature cells in the circulating blood, yet so far as nucleated red cells are concerned there is absolutely no evidence of such a process, and in the case of reticulocytes the evidence is equivocal. In figs. 12 and 13 the proportion of these two types of cell in the foetus of varying degrees of maturity and in the newborn of different ages is shown. So far as nucleated red cells are concerned it is seen that there is a steady fall in their proportion during foetal life and that, unless during the first few hours of life, they are hardly ever seen in the post-natal state. The only case in which these were observed after the first day of life was an Rh+child whose mother was Rh−. The reticulocytes also fall during the later weeks of foetal life, but after birth there occurs a temporary rise on the third and fourth days. This might be taken to indicate the presence of increased haemolysis, but the rise is very slight and only affects a minority of infants, so that it is questionable if any significance can be attached to it.

EXPERIMENTAL APPROACH TO THE PROBLEM. Goldbloom and Gottlieb (1930) have attempted to solve the problem of increased haemolysis during the neonatal period by experiments on the guinea-pig. Guinea-pigs were placed in chambers under minus (reduced) pressure to simulate the hypothetical conditions of life *in utero*. These authors found that in consequence of this procedure both haemoglobin and red cells rose by 30 per cent. They state that, when the guinea-pigs were removed from the chamber, which was considered analogous to birth, the haemoglobin and red-cell values fell, reaching the normal level within five days, and that at the same time the icteric index rose at once from nil to 1·5 units. It was also noted that the marrow became hyperplastic during the period the animals were under the influence of diminished atmospheric pressure. These authors lay great stress on their findings and certainly at first sight it does look as if the experimental conditions and those pertaining to our problem are identical. But a scrutiny of the experimental protocols raises doubts regarding their accepted significance. For instance, in three of the eleven experiments the plasma bilirubin was raised while the animals were still in the chamber, and in the other eight animals, although the plasma bilirubin was not noted to be raised till after their removal from the influence of the diminished atmospheric pressure, the maximum level was observed immediately after removal from the chamber and it fell rapidly thereafter. This is, of course, exactly the opposite of what obtains during infancy, when the plasma bilirubin almost invariably rises after birth. There is also

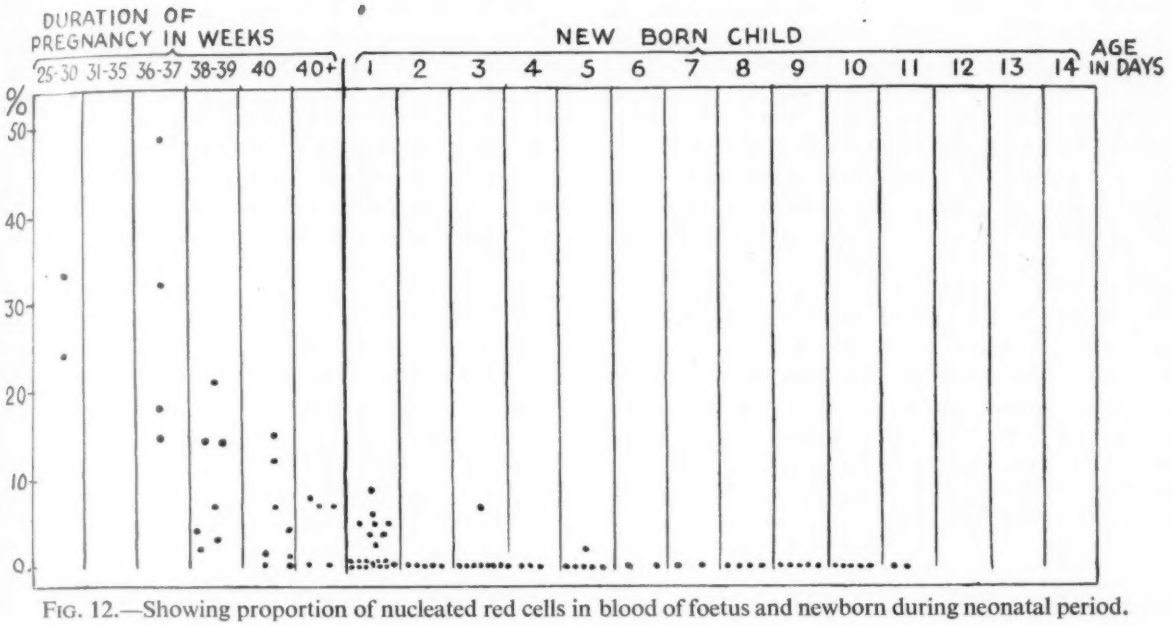

FIG. 12.—Showing proportion of nucleated red cells in blood of foetus and newborn during neonatal period.

the fact already noted (p. 196) that the red-cell and haemoglobin concentrations also rise. It would seem, therefore, that the increased haemolysis in Goldbloom and Gottlieb's experiments is related to hyperpoiesis (the greater the number of red cells the greater will be the number undergoing natural death or haemolysis at any particular moment), and that the fall in red-cell concentration is due more to a slowing down of haemopoeisis due to a return to a normal state of the hyperplastic marrow after removal of the stimulus (rarified atmosphere) than to any increased haemolysis. Indeed, these experimental findings are exactly parallel with the clinical changes described in individuals resident at high altitudes (Hurtado, 1932 and 1937; and Monge, 1937) but they are certainly not analogous to what obtains in the newborn child.

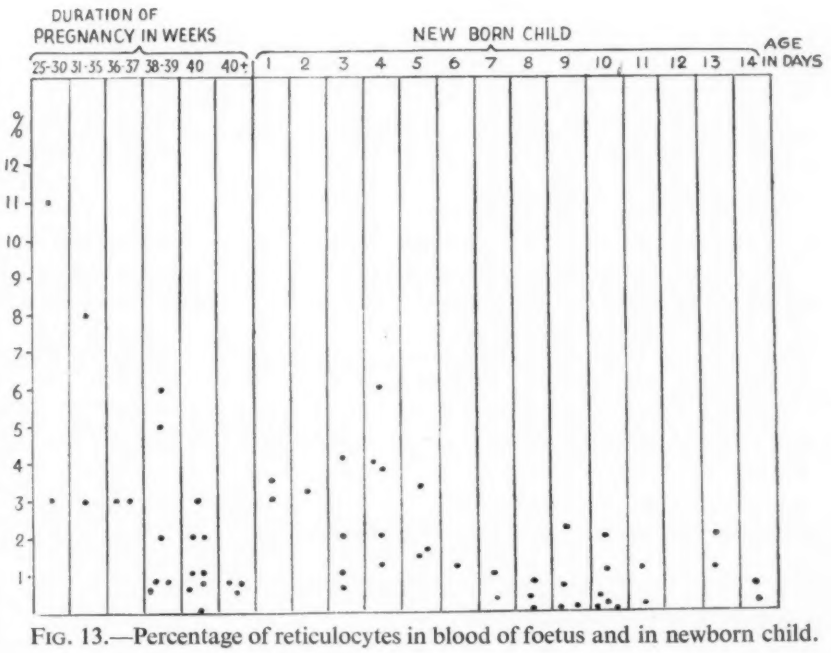

FIG. 13.—Percentage of reticulocytes in blood of foetus and in newborn child.

Part 2: The Blood during Later Infancy

THE EFFECT OF THE ADMINISTRATION OF IRON. It has always been recognized that the concentration of haemoglobin and red cells is less during the latter part of the first year of life than during later childhood and adult life. With the fall during the neonatal period the haemoglobin may reach a reading between 60 and 70 per cent. and the reds a level of 3·5 million per c.mm., but with the recovery, which sets in during the third and fourth months, readings of between 70 and 80 per cent. of haemoglobin and of 4·5 million red cells per c.mm. are reached. Details of the findings in my examples of full-time children are given in tables 3 and 4, and the averages of both full-time and premature children are represented graphically in figs. 14 and 15.

Until 1931 this lower level of haemoglobin and red cells during later infancy was considered physiological and thus unalterable. But in that year Helen Mackay (1931) stated that by the addition of an iron salt to the infant's diet the haemoglobin could be raised 5 or 10 per cent. higher, and naturally she postulated that the lower level was the consequence of a nutritional defect, a view which would seem to be fairly generally accepted.

There is no doubt that in what we consider the natural food of the infant (breast milk)—and the same is equally true of the substitute food (cow's milk)—there is an insufficient amount of iron to supply the child's current needs. On the basis that Nature seldom makes mistakes, it is generally held that she circumvents this shortage of iron in the infant's diet by sending the child into the world with a store of iron in the liver, a store which is said to be laid down for the most part during the last three months of pregnancy. It was by this device that, in spite of the dietary deficiency, the full-time child was considered to be satisfactorily provided for, but doubts prevailed regarding the case of the premature child. Indeed, it is almost universally taught that the premature infant, unless given additional iron, will develop anaemia. My researches, however, raise doubt concerning the validity of such a doctrine.

We do not know how long Nature intends breast milk to be the sole means of nourishment, but if we are correct in assuming that it should be continued till the appearance of teeth, as is done to-day, then we should desire strong proof that all the child's nutritional requirements are not being supplied. Yet on the strength of the work of Helen Mackay and her collaborators very far-reaching conclusions have been drawn not only regarding the provisions of Nature but also concerning the incidence of anaemia in infancy and childhood. I have not, in surveys undertaken in such diverse localities as Glasgow, the east end of London (1937), and the city of Oxford, been able to detect the widespread anaemia which Mackay (1942) and some other observers have found.

Four years ago (1942), in a discussion on nutritional anaemia at the Royal Society of Medicine, in a communication entitled *The Blood as an Index*

TABLE 3

AVERAGE RED CELLS IN A TREATED (RECEIVED IRON) AND A CONTROL GROUP OF CHILDREN, ACCORDING TO AGE

Age in months	Without iron			With iron			Size of difference
	No.	Mean	C.V.	No.	Mean	C.V.	
0–1	7	5·514±0·159	7·65	8	5·76 −0·414	20·30	P=0·9
1–2	7	4·657±0·218	12·39	15	4·413−0·136	11·90	P=<0·4>0·3 (n.s.)
2–3	7	4·143±0·244	15·57	16	3·869−0·113	11·708	P=<0·1>0·05 (n.s.)
3–4	8	4·113±0·122	8·36	15	3·913−0·085	8·43	P=<0·7>0·6 (n.s.)
4–5	8	4·288±0·104	6·88	16	4·38 −0·094	8·607	P=<0·4>0·3 (n.s.)
5–6	10	4·220±0·081	6·09	12	4·36 −0·075	6·078	P=<0·3>0·2 (n.s.)
6–7	9	4·467±0·096	6·42	13	4·39 −0·114	9·362	P=<0·7>0·6 (n.s.)
7–8	11	4·273±0·057	4·45	15	4·31 −0·127	11·38	P=<0·3>0·2 (n.s.)
8–9	7	4·257±0·174	10·83	16	4·23 −0·096	9·031	P=<0·3>0·2 (n.s.)
9–10	7	4·171±0·099	6·30	15	4·16 −0·092	8·53	P=<0·9>0·8 (n.s.)
10–11	11	4·345±0·164	12·54	16	4·23 −0·085	7·99	P=0·8 (n.s.)
11–12	7	4·443±0·180	10·71	16	4·025−0·104	10·31	P=<0·6>0·5 (n.s.)
12–13	13	4·354±0·140	11·621	13	4·307−0·043	3·60	P=<0·02>0·01(sig.)

n.s. =not significant.
sig.=significant.

TABLE 4

AVERAGE HAEMOGLOBIN IN A TREATED (RECEIVED IRON) AND A CONTROL GROUP OF CHILDREN, ACCORDING TO AGE

Age in months	Without iron			With iron			Size of difference
	No.	Mean	C.V.	No.	Mean	C.V.	
0–1	7	122·0±5·45	11·8	8	123·50−10·63	24·31	P=<0·7>0·6 (n.s.)
1–2	8	95·0±5·68	16·9	15	89·9−3·01	13·0	P=<0·4>0·3 (n.s.)
2–3	7	84·6±6·51	20·4	16	74·1−2·28	12·3	P=<0·3>0·2 (n.s.)
3–4	8	78·0±3·19	11·6	15	76·5−1·51	7·6	P=<0·2>0·1 (n.s.)
4–5	8	80·5±2·26	7·9	17	83·4−1·84	9·1	P=<0·6>0·5 (n.s.)
5–6	10	81·0±1·09	4·2	12	83·2−1·49	6·2	P=<0·3>0·2 (n.s.)
6–7	9	82·2±1·90	6·9	13	83·4−1·54	6·7	P=<0·7>0·6 (n.s.)
7–8	11	76·7±2·29	9·9	15	80·9−2·38	11·4	P=<0·9>0·8 (n.s.)
8–9	8	77·0±1·46	5·4	16	81·0−2·25	11·1	P=<0·9>0·8 (n.s.)
9–10	7	80·6±1·29	4·2	15	79·9−2·24	10·9	P=<0·9 (n.s.)
10–11	11	79·1±2·83	11·9	16	80·0−1·93	9·7	P=<0·5>0·6 (n.s.)
11–12	8	74·4±2·75	10·5	16	77·1−2·73	14·1	P=<0·05>0·02 (border-line sig.)
12–13	13	75·8±2·12	10·1	13	83·2−1·72	7·4	P=<0·8>0·7 (n.s.)

n.s.=not significant.
sig.=significant.

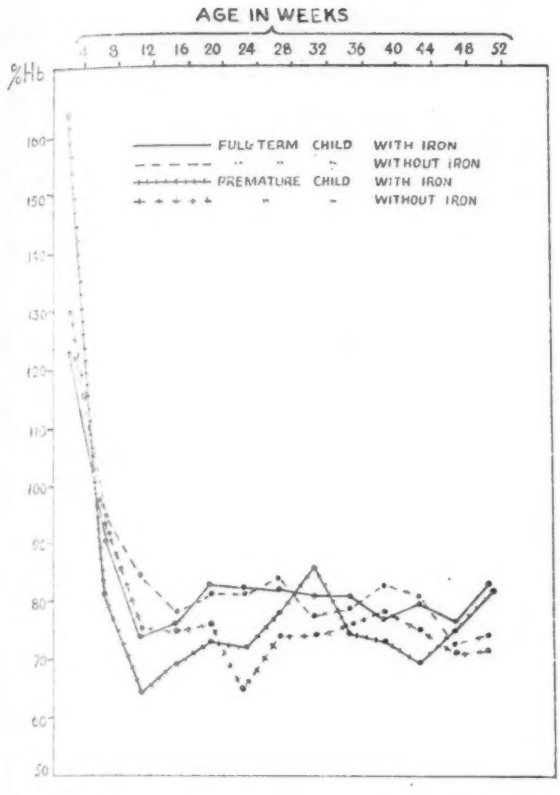

FIG. 14.—Haemoglobin percentage concentrations in full-term and premature children with and without additional iron.

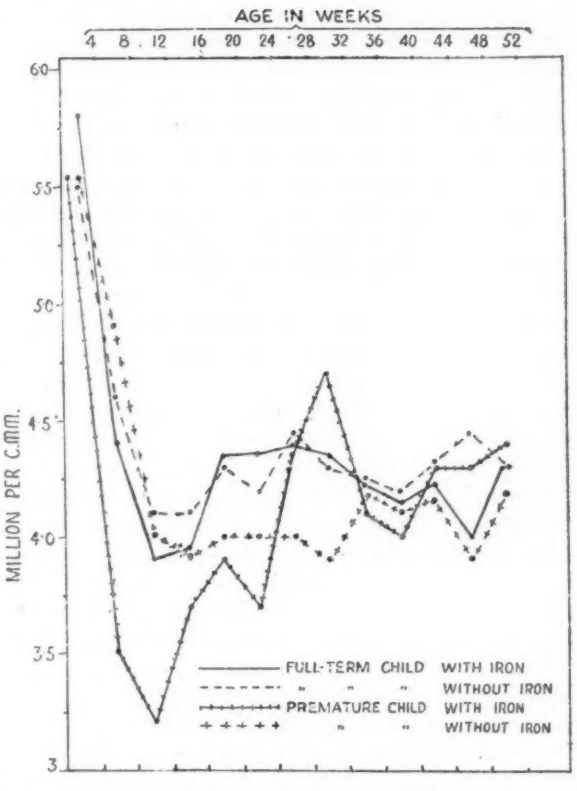

FIG. 15.—Red-cell concentrations in full-term and premature children with and without additional iron.

of Health, I put forward the thesis that it is fallacious to look upon the concentration of the haemoglobin and red cells in the blood as a direct measure of the health of the individual.

My attention had been first drawn to this matter during a research (1909) on the blood in rickets, when I found that, both in experimental rickets in the dog and in spontaneous rickets in the child, the concentration of the haemoglobin and red cells was increased. I found, for example, higher haemoglobin and red-cell levels in rachitic children resident in the Glasgow slum than in the healthy children of the wealthy citizens living under good conditions in the suburbs. I was inclined to ascribe this state of affairs to the fact that the rachitic child was confined in a badly ventilated house and thus required additional oxygen carriers, just as is the case in the individual living at a high altitude in a rarified atmosphere. One is here tempted to recall the observation of Dobbs (1942) that nurses evacuated from London to the country at the beginning of the war showed a fall in the haemoglobin level. This phenomenon Dobbs attributed to less satisfactory dietetic conditions in the country than in the town, but in my view it may possibly have been due to the result of improved atmospheric conditions and a consequent lesser demand for oxygen carriers. Is it not possible that in this way also we can account for the different haemoglobin levels in childhood, in women, and in men? In this order we can express the relative expenditure of muscular energy, and thus the relative amount of oxygen required and the consequent relative amount of oxygen carriers.

For some years, too, I (1942) had been studying the effect of the administration of iron to normal individuals, apparently concurrently but unknowingly with my American colleagues, Fowler and Barer (1941). We all came to the same conclusion—that it was impossible to increase, unless very temporarily, the haemoglobin level in the healthy individual by the administration of iron.

For these reasons I was pleased to have the opportunity, provided by Prof. Chassar Moir and Dr. R. G. Macfarlane, to contrast the blood curves in full-time healthy infants, and also in premature but otherwise healthy babies, with and without iron added to their diet. I began observations on many infants, but a considerable number of the mothers failed to co-operate for a sufficient length of time, and I have been left with twenty-six full-time, and ten premature children. I was particularly anxious to study this problem in a series of twins, as they would seem to provide the most uniform material for test-case and control, but unfortunately it was here that co-operation was least satisfactory, and my material is insufficient for analysis.

I found no radical difference between the sexes, and so for purposes of simplification have combined the sexes on the graphs. For the differentiation between full-time and premature babies, I have depended on the duration of pregnancy and have not adopted the more recent index—birth weight—

as indicating the degree of maturity. In most instances the mothers had attended the ante-natal clinic at the hospital, and thus there was a fair measure of certainty regarding the duration of pregnancy. All the premature babies in my series receiving additional iron had a birth weight under 5½ lb. (they ranged from 2·9 to 5·2 lb.) and thus would be considered immature by modern classification; but, by an unfortunate coincidence, of the five premature babies chosen as controls—that is, not given additional iron—three had birth weights above 5½ lb. However, a comparison between the three over 5½ lb. and the two under 5½ lb. reveals no radical difference in the trend of the various curves, so that there seems no disadvantage in adopting the time factor rather than the weight factor.

I examined fewer infants than Helen Mackay; but all the children were healthy and the administration of iron was begun within ten days of birth. I usually started with daily doses of 20 mg. of iron in the form of ferrous sulphate, and gradually increased the amount to 60 mg., and in some cases to 120 mg. per day. In Helen Mackay's (1931) series the children were selected from her out-patient clinic and ' in many cases were ill and in the majority of instances were underweight and underfed.' Moreover, they were not infrequently five months, and in some instances were eight months old, when they first came under observation. Mackay states that the daily dose of iron in her cases varied between 60 and 120 mg. per day and was given in the form of ferri et ammon. citrate.

Figure 16, showing the average weight curves, reveals the satisfactory and almost equal rate of growth in all the various groups of children in my series. The parallelism of the average weights of the full-time children receiving added iron and those not so treated is striking. Those not receiving iron start at a slightly lower level but they do not lag behind those receiving iron. In the case of the premature children, those receiving iron started at a much lower level than those not receiving iron, and their rate of increase is certainly more rapid, but the rate of growth of those not receiving iron is quite as good as that of the normal full-time child.

The percentage concentration of haemoglobin and red cells in full-time children with and without additional iron are given in tables 3 and 4. These tables were compiled from my findings by Dr. Russell of the Department of Social Medicine, Oxford, and from the statistical analysis there emerges no significant differences between the two groups. In the graphic representation of the means of the two groups, shown in figs. 14 and 15, it will be seen that in the group receiving iron there is a more rapid recovery, specially marked in the case of the red cells, and by the age of five months higher haemoglobin and red-cell concentrations are reached in the group of children receiving added iron than is the case in the control series of children. But this higher level is only temporary and is not sustained, so that by the end of their first year, although the

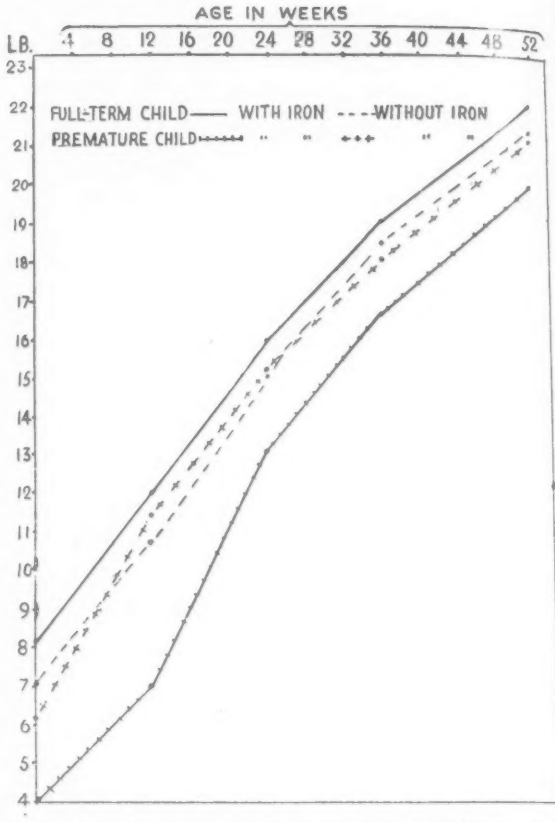

FIG. 16.—Average weight curves of full-term and premature children with and without iron.

administration of iron had been without intermission, there is no difference between them. This recalls what I, and also Fowler and Barer, have found to be the result of the administration of iron to healthy older children and adults, viz., a temporary stimulating effect on haemopoiesis, but one to which the body soon becomes acclimatized.

As in the case of the full-term child, so in that of the premature child there is little difference in haemoglobin and red-cell concentrations in the group receiving additional iron and in the control group not receiving iron. The more rapid recovery, particularly of the red cells, after the neonatal fall is also apparent in the premature children receiving iron, but here again the superiority is only temporary, and by the time the children are one year old there is no significant difference between the groups (figs. 14 and 15).

Nor are any radical differences in the rate of blood formation apparent between the children receiving additional iron and those not so treated, when we study the total blood haemoglobin and red-cell contents. This we have attempted, as already mentioned, by computing from the blood counts and the body weights the total haemoglobin and red-cell contents. The average figures are shown in figs. 17 and 18, which reveal an almost uninterrupted rise in all (prematures and full-term alike) after the preliminary neonatal fall. In the case of the full-term children, those receiving iron present consistently—but only slightly—higher total

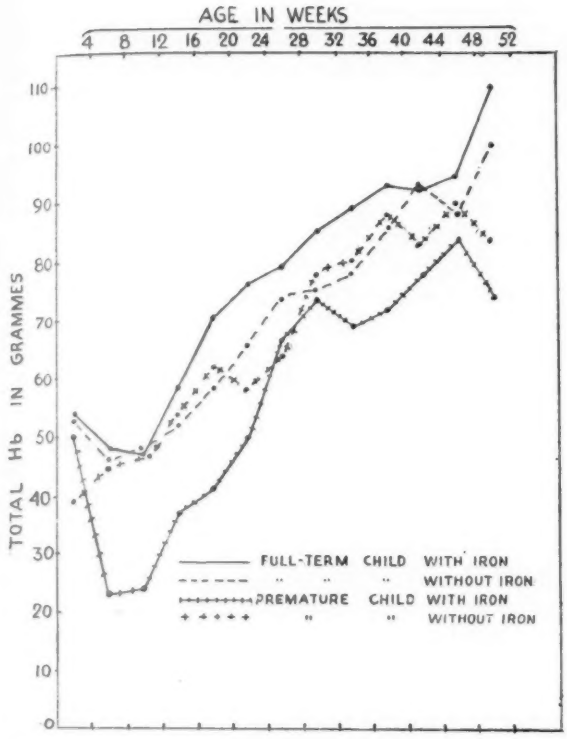

FIG. 17.—Average total Hb in grammes in full-term and premature child.

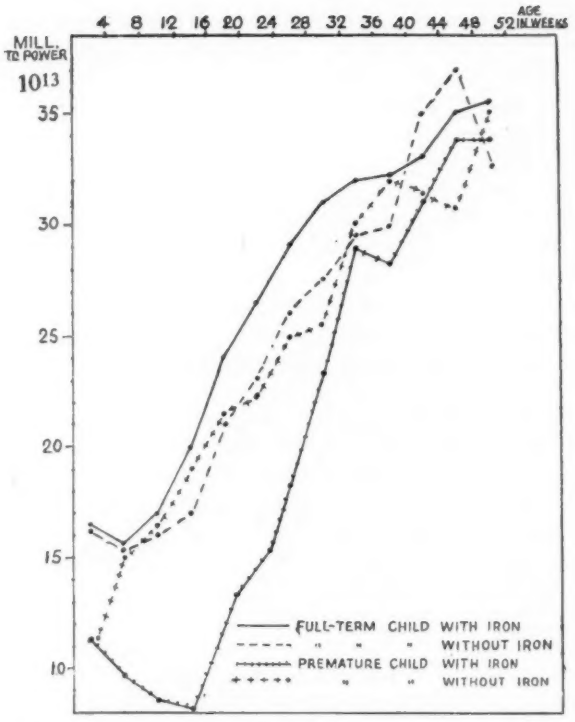

FIG. 18.—Total red cells in full-term and premature child with and without iron.

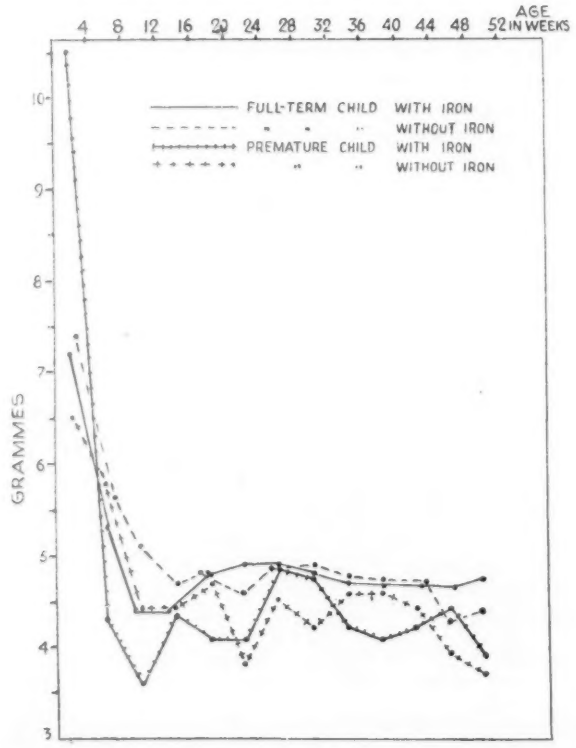

FIG. 19.—Hb in grammes per lb. weight in full-term and premature child with and without iron.

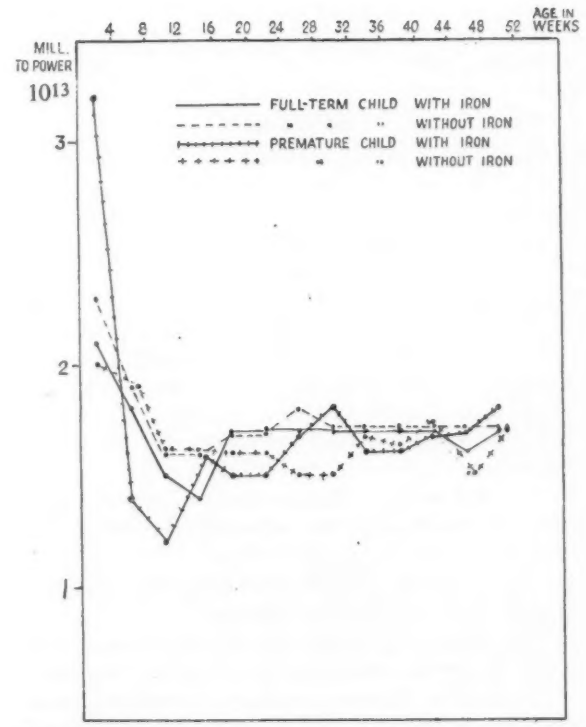

FIG. 20.—Red cells in millions to 10^{13} power per lb. weight in full-term and premature child with and without iron.

haemoglobin and red-cell values than those not receiving iron, but by the time the children are one year old there is no significant difference between the two groups. Most remarkable is the behaviour of the curves in the case of the premature children. In those not receiving additional iron the total amounts of haemoglobin and number of red cells is little different from that of the full-time child not receiving iron, and in the group receiving additional iron there did not occur any apparent diminution in total haemoglobin and reds during the neonatal period. The most striking feature of these charts is the steady and satisfactory formation of blood in all the groups.

BLOOD HAEMOGLOBIN AND RED CELLS PER LB. WEIGHT. During my analysis of the findings it occurred to me that it would be interesting to refer the amount of blood haemoglobin and number of red cells to body weight. This relationship is shown in figs. 19 and 20, in which haemoglobin and red cells are expressed in amount per lb. weight. The similarity of the curves of the various groups (full-time and premature alike) is striking. Unless in the case of haemoglobin in the premature children, which runs at a slightly lower level than in the full-time children, there is no radical difference between them.

A survey of the above findings leads to the conclusion that iron is not necessary as an adjunct to the diet of the normal infant for normal blood formation, that its administration does not lead to any improvement in the state of the blood, unless temporarily immediately after its presentation, when it seems to exert merely an irritating effect on the haemopoeitic tissue just as it does in the case of the normal adult. Nor does there seem any evidence that additional iron is necessary even in the case of the premature child.

Conclusions

1. The haemoglobin and red-cell concentrations are lower in the foetus than in the child.

2. The haemoglobin and red-cell concentrations increase considerably within the first few hours after birth. For this no adequate explanation can be given.

3. After the initial post-natal increase in haemoglobin and red-cell concentrations, there is a gradual fall during the first three months of life.

4. This post-natal fall in haemoglobin and red-cell concentrations is most rapid during the second week of life.

5. The fall in the haemoglobin and the red cells during this period is not absolutely parallel: the fall in haemoglobin concentration is more marked than the fall in the red-cell concentration and causes a change in their relative proportions.

6. The change in proportion of haemoglobin and red cells is due to a change in the size of the red cell—which is smaller during post-natal than during antenatal life—and it indicates considerable new blood formation.

7. The total haemoglobin and red-cell contents of the circulation show the same trend as the haemoglobin and red-cell concentrations, but the fall in the total amounts is less marked and continues for a shorter period.

8. There is no evidence of increased haemolysis during the neonatal period, in fact, rather the reverse.

9. Increased haemolysis is, therefore, not the prime factor in the causation of icterus neonatorum.

10. The fragility of the red cell in the newly born is diminished in comparison with that during foetal life and later childhood.

11. Nucleated red cells and reticulocytes, while abundant during foetal life, rapidly disappear from the circulation in the newborn child. Their persistence suggests some abnormality, e.g. the presence of the Rh factor.

12. Goldbloom and Gottlieb's experiments with the guinea-pig in a rarified atmosphere reproduce the results from living at a high altitude, but they are not comparable with those due to the change-over from foetal to post-natal existence.

13. The administration of iron to the diet of the full-time and premature healthy child causes a slightly earlier and higher post-neonatal rise in both haemoglobin and red-cell concentrations than occurs without any medication.

14. The improvement in the haemoglobin and red-cell concentrations from the administration of iron in the full-time and premature healthy infant is only temporary: by the time the children are one year old there is no statistical difference between the blood pictures of the treated and the untreated infant.

15. Estimations of total haemoglobin and red cells in the full-time and premature healthy infant reveal a progressive increase in the amount of haemoglobin and number of red cells from the second month of life, and show that the increase in both haemoglobin and red cells is identical in infants receiving additional iron and in those not receiving additional iron.

16. The effect of iron added to the diet of the normal infant, full-time and premature, would seem to be the same as in the case of the healthy older child and adult, viz., a temporary irritation of haemopoietic tissue.

REFERENCES

Dacie, J. V., and Vaughan, J. M. (1938). *J. Path. Bact.*, **46**, 341.

Dobbs, R. H. (1942). *Proc. roy. Soc. Med.*, **36**, 81.

Findlay, L. (1909). *Lancet*, **1**, 1,164.

—— (1937). *Brit. med. J.*, **1**, 12.

—— (1942). *Proc. roy. Soc. Med.*, **36**, 75.

—— (1945). *Arch. Dis. Childh.*, **20**, 64.

Fowler, W. M., and Barer, A. P. (1941). *Amer. J. med. Sci.*, **201**, 642.

Goldbloom, A., and Gottlieb, R. (1930). *J. clin. Invest.*, **8**, 375.

Hurtado, A. (1932). *Amer. J. Physiol.*, **100**, 487.

—— and others (1937). *Amer. J. med. Sci.*, **194**, 708.

Mackay, H. M. M. (1931). *M.R.C., Spec. Report Series*, No. 157.

—— (1942). *Proc. roy. Soc. Med.*, **36**, 69.

Monge, C. (1937). *Arch. intern. Med.*, **59**, 32.

BILIARY OBSTRUCTION ASSOCIATED WITH ICTERUS GRAVIS NEONATORUM

BY

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For twenty years it has been known that obstructive jaundice may occasionally be seen in icterus gravis neonatorum. Still (1927) quoted the view that the bile of excessive haemolysis becomes too viscid to pass freely along the ducts, and he mentions the low pressure at which it is secreted. This view does not altogether explain the facts, because a marked obstructive phase does not necessarily go with the greatest haemolysis or the deepest preceding jaundice. MacClure (1931) suggested that the presence of a foreign substance in the bile caused coagulation in the bile capillaries. We favour a third possibility—namely, that biliary obstruction is due to swelling of damaged hepatic cells—because histological studies of icterus gravis show that such an association exists. The association is seen also in conditions other than icterus gravis, for example, stagnation of bile may be seen just outside areas of maximal necrosis in infective hepatitis.

Skelton and Tovey (1945) postulate two forms of biliary obstruction in association with icterus gravis: (a) blockage of one of the larger bile ducts with inspissated bile; and (b) conversion of the bile ducts into a fibrous cord. First let us consider the latter, that is, atresia of the bile ducts associated with icterus gravis.

Biliary Atresia Associated with Icterus Gravis Neonatorum

Pasachoff (1935) reported the case, fatal at the age of five days, of a coloured girl who some twelve hours after birth had deep jaundice, hepatosplenomegaly, and erythroblastosis, yet no anaemia. On the fourth day haemorrhage appeared and the stools were white. A moderate degree of anaemia developed. Necropsy showed extensive extramedullary haematopoiesis, kernikterus, complete atresia of the bile ducts, and cerebral aplasia. This case was reported in the pre-Rh period, and, therefore, the diagnosis of icterus gravis, though probably correct, could not be established beyond all doubt.

H. N. Sanford (1940) reported the case of an infant who at the age of two hours had marked anaemia (red blood cells 1,600,000 per c.mm.) and erythroblastosis (nucleated red blood cells 162,000 per c.mm.). The icteric index was 500 units (35 mg. per 100 c.cm.). Professor Sanford kindly sent the pathologist's report to one of us (R. L.) and we quote: 'The whole of the gall-bladder is slightly thickened and the lumen contains approximately 1 c.cm. of thick stringy bile; practically complete stenosis is seen, and this is traced to the ampulla of Vater. A probe can be inserted into the ampulla for a distance of three millimetres. The cystic duct is so small that a small probe cannot be passed. The same is true of the patent common duct. The lumen of the common bile duct is a few millimetres in diameter.' The mother was Rh-negative, the father Rh-positive, and another child born two years later also Rh-positive; this one developed a typical erythroblastosis foetalis at birth. Sanford concludes that the first baby was a case of 'atresia' of the bile ducts associated with erythroblastosis foetalis yet we cannot entirely concur with this view. It appears from the pathologist's report that this was not a case of atresia of the bile ducts but one with some degree of stenosis, which is not very infrequent. Again, the diagnosis of erythroblastosis foetalis, since it occurred in the pre-Rh period, was not quite proven. The latter child of this family was tested for the Rh factor and the mother found to be Rh-negative, but there is no report that she developed anti-Rh agglutinins.

Skelton and Tovey (1945) report two cases of erythroblastosis foetalis associated with congenital atresia of the bile ducts:

FAMILY G. E. The patient, a second child (the first was normal), developed jaundice on the first day, passed bile in the urine, and died aged two days; no blood count was reported. Necropsy disclosed erythroblastosis, marked erythropoiesis in the liver and spleen, fibrous obliteration of the common bile duct, and kernikterus. The father was Rh-positive; the child's Rh factor was not examined (this was in 1942). The first-born child was subsequently examined and found to be Rh-positive, the mother was Rh-negative, and no antibody was demonstrable three years after the birth of the affected child.

COMMENT. We think that in this case no final proof of the association of the two conditions has

been given. The child was not tested for the Rh factor, anaemia is not mentioned as a clinical feature, no Rh antibodies were found in the mother's serum three years after the birth of the child, and the mother's serum was apparently not tested at the time when antibodies could reasonably be expected. None of the necropsy findings (erythroblastosis, extra-medullary erythropoiesis, or kernikterus) are absolutely pathognomic of icterus gravis, though they are all highly suggestive.

FAMILY M. The patient, a second child (the first being born normal and now alive and well) had jaundice on the first day, with bile in the urine, and clay-coloured stools. Cholecysto-gastrostomy, performed for fibrous occlusion of the common duct, was followed by recovery. This child was Rh-positive, and its father Rh-positive. Its mother Rh-negative. The mother's serum was not was examined for agglutinins at the time of the infant's illness, but they were present in the mother's blood at the third and fourth pregnancies, which resulted in two babies with erythroblastosis foetalis; these died at the age of four and three days respectively, both with kernikterus.

COMMENT. No suggestion has ever been made that this second child in that family was a case of erythroblastosis foetalis. It has been suggested, however, that it was a case of atresia of the common bile duct. Though we do not know all the clinical details, we venture to suggest that the diagnosis of atresia of the bile duct at operation is often difficult to make. To illustrate this point we would like to mention a recent case in which an experienced paediatric surgeon was concerned. This was a patient, aged one month, with obstructive jaundice from the age of four days, and cholecysto-gastrostomy was performed. At necropsy twenty-four hours after operation the bile ducts were patent, and the obstruction was found to be due to liver cirrhosis of obscure nature, Rh incompatibility having been excluded. But assuming that atresia was present in the second child in Family M, there is no reason why congenital atresia of the bile ducts and icterus gravis should not occur in different children of the same family. For these reasons we consider that a direct association was not established in Family M.

The same authors go on to quote a third family of six children, the fourth of which died from congenital obliteration of the bile duct. Its Rh factor was not examined. The sixth child died from erythroblastosis foetalis, Rh antibodies having been present in the mother's blood at the sixth pregnancy. This again appears to be a case of the two conditions, biliary atresia and erythroblastosis, occurring in different children of one family.

We have been unable to find any more reports in the literature of the association of erythroblastosis and congenital atresia, but we now mention a patient who has come under our observation through the courtesy of Dr. Donald Paterson, yet again there was no absolute proof of the association of the two conditions.

M. S., a male baby (two siblings are alive and well and had no neonatal jaundice or anaemia), developed jaundice from the third day which lasted eight days. When six weeks old he had bruising and became anaemic. The jaundice recurred at the age of seven weeks and increased in depth. At eight weeks the liver was found to be enlarged, the spleen was not palpable, and the blood count was 1,500,000 erythrocytes per c.mm. Haemoglobin was 4·8 g. per cent., and two normoblasts were found per 100 white blood cells. The white blood count was 20,600 per c.mm.; van den Bergh 6·7 mg. per 100 c.cm. Urine contained bile pigment. The faeces were very pale. Rh investigations carried out when the baby was nine weeks old showed the baby to be Rh-positive and the mother Rh-negative. No anti-Rh agglutinins were present in the mother's serum. The child was given a blood transfusion of Rh-negative group O blood, and the blood count rose to 5,900,000 erythrocytes per c.mm. When aged four months and still deeply jaundiced, the child was admitted to the Hospital for Sick Children, Great Ormond Street. His blood count was then 5,700,000 per c.mm. (no normoblasts). Haemoglobin was 16·1 g. per cent. The Rh investigations were repeated and confirmed. A laparotomy was performed; the gall-bladder was found to be solid and rubbery and the liver large and cirrhotic, and no bile ducts suitable for anastomosis were found. The child died seven days later at the age of four and a half months. The liver was found to be cirrhotic. Bile plugs were found in the intercellular bile canaliculi. The epithelium of the intrahepatic bile ducts was normal. No extramedullary erythropoiesis was noted. The gall-bladder was small and contained very little white bile. The cystic duct and common bile duct were occluded. The hepatic ducts appeared to be patent but were very narrow. The spleen was much enlarged and showed a marked increase of fibrous tissue.

COMMENT. In this case there was early neonatal jaundice; at two months there was recurrence of the jaundice, which was clinically obstructive in type; there was late onset of a severe anaemia, and later still cirrhosis of the liver and intercellular bile thrombi. Though the mother was Rh-negative and the infant Rh-positive, no evidence of Rh immunization was found in the mother's serum when the infant was nine weeks old; so that in this case of biliary atresia there is again no proof of erythroblastosis foetalis due to Rh incompatibility.

Discussion

The above survey of cases coming under Skelton and Tovey's Type B of biliary obstruction associated with icterus gravis leads us to the conclusion that in no instance has a direct etiological association been proved beyond doubt, though some cases have been highly suggestive of this association.

We have also considered eight cases of atresia of the bile ducts which have been tested in regard to the Rh factor at the Hospital for Sick Children, Great Ormond Street. No evidence of Rh isoimmunization was obtained. The series is very small, but certainly lends no support to the idea that Rh incompatibility is an etiological factor in congenital atresia of the bile ducts.

Biliary Obstruction in Icterus Gravis Neonatorum without Atresia of the Bile Ducts

In this type of biliary obstruction in icterus gravis we include both intrahepatic and extrahepatic obstruction other than atresia of the bile ducts. Skelton and Tovey's Type A, i.e. blockage of one of the larger bile ducts with inspissated bile, is included in this group.

The jaundice of icterus gravis is mainly haemolytic, though an obstructive element is sometimes present as well. When there is obstruction it usually occurs as an evanescent phase, though there have been occasional cases reported in the literature with the period of obstruction lasting for several months. Serological testing has added so much to the accuracy of diagnosis that we propose to confine ourselves to cases which have been reasonably established by Rh investigations. They may show an early onset of an obstructive phase which may be continuous for several weeks or months, or an evanescent phase of haemolytic jaundice with a recurrence of the icterus after a few weeks, and then biliary obstruction, usually partial, lasting for several more weeks. This sequence is illustrated by the following case (Lightwood, 1943).

Case 1. A. C., a male, was a second child. The only sibling, aged four years, was jaundiced for the first three to four days of life, but is now healthy.

Jaundice appeared twenty-four hours after birth and lasted fourteen days; pallor was not noted; the stools were normal. Ten days later, at the age of three and a half weeks, the stools became pale and the urine dark. During the next week the baby became increasingly pale and jaundiced (greenish tinge). One week later still he was seen at hospital with jaundice, anaemia, abdominal distension, prominent veins of the abdominal wall, and ascites (making palpation of the liver and spleen impossible). The stools were pale and the urine dark, and the diagnosis between icterus gravis and congenital atresia of the bile ducts was not easily made. The blood picture did not decide the diagnosis: haemoglobin was 85 per cent., and red blood cells 3,480,000 per c.mm., the colour index 1·3, and white blood cells 22,600 per c.mm. Erythroblastaemia was not present and would not have been likely to persist so late. The icterus index was 50. The direct van den Bergh reaction was positive, and the indirect reaction 10 units. Wassermann reaction and Kahn reaction of mother and baby were negative. Rh tests, however, showed the baby to be Rh-positive; his mother was Rh-negative, and her blood contained Rh antibody. Therefore the diagnosis of icterus gravis was established.

The infant was gravely ill, and the abdomen needed paracentesis on two occasions, 10 oz. and 20 oz. being withdrawn. The haemoglobin fell to 60 per cent., and an Rh-negative blood transfusion of 150 c.cm. was given. Thereafter the haemoglobin level was well maintained. Owing to the prolonged jaundice and the presence of such considerable ascites, the prognosis seemed bad, but after paracentesis and blood transfusion the child began to improve. Subsequently he gained weight satisfactorily, and ascites and jaundice slowly disappeared during the next six weeks. This was after an obstructive phase lasting eleven weeks. Even after this there were slight recurrences of obstruction of some two days' duration (two attacks).

Case 2. D. K., a male, aged eleven hours, was admitted to the Hospital for Sick Children, Great Ormond Street, under Dr. W. G. Wyllie, with marked jaundice and hepatosplenomegaly. Birth weight was 7½ lb. The child had asphyxia (the cord was wound twice round the neck), but revived with lobelin.

Two siblings, aged seventeen and fourteen years, were alive and well. The third child of the family died with jaundice at the age of eighteen days. The fourth child miscarried, and the fifth was the patient. On examination, orange-yellow jaundice was noticed, and the liver was palpable three fingers' breadth below the costal margin; the spleen was palpable. Red blood cells were 3,960,000 per c.mm., with 92 normoblasts per 100 white blood cells. The baby was Rh-positive; the mother was Rh-negative, and one week after delivery her serum contained Rh antibody of a titre 1 in 64. At two days old, 205 normoblasts were found per 100 white blood cells. Subsequently the normoblast count decreased gradually. The urine contained bile pigment, and the stools were pale. At one week of age the serum bilirubin was 28·5 mg. per 100 c.cm. At three weeks of age the alkaline plasma phosphatase was 18·4 units per 100 c.cm. (normal 10–20 units). This was taken as an indication against extrahepatic obstruction, and, therefore, no laparotomy was performed. The obstructive jaundice lasted about four months. When seen, at five months, the infant was feeding and gaining well. The jaundice had completely disappeared, and the van den Bergh reaction in the serum was negative.

The clinical histories just given do not explain the mechanism of obstruction. In contrast, the following cases, coming to necropsy, throw light on the pathology underlying the obstructive phase of erythroblastosis foetalis for they show that at least two states may be found at necropsy, (a) pigment stones, and (b) cirrhosis.

A. Pigment Stones causing Extrahepatic Obstruction

Case 3. A. H., a male, aged four and a half months, came under the care of Dr. Donald Paterson at the Hospital for Sick Children, London. His seven-year-old brother had had no jaundice, but a three-year-old brother had had jaundice from the third to the fourteenth day after birth. The patient had had a normal birth (weight 7 lb. 8 oz.), was breast-fed for three days, and had a 'septic' umbilicus until two months old. There was no neonatal jaundice, but jaundice from two and a half months without constitutional disturbances; stools were pale with a yellow tinge, and the urine was dark and contained bile pigment; there was no vomiting, and he was taking his feeds well. When admitted to hospital he had marked jaundice. The liver could be felt one and a half fingers' breadth below the costal margin. The spleen was not felt. Heart and lungs were normal. Red blood cells were 5,120,000 per c.mm. of blood, haemoglobin 110 per cent. (15·4 g. per 100 c.cm.), reticulocytes 1·4 per cent., and there were no nucleated red cells. White blood cells were 14,000 per c.mm. with 69 per cent. lymphocytes. The baby was Rh-positive, the

mother Rh-negative, with anti-Rh agglutinins (titre 1 in 32). The blood Wassermann reaction of the mother was negative. Liver function tests were as follows; van den Bergh, immediate direct positive; quantitative, 8·6 mg. per 100 c.cm. (normal up to 0·5 mg.). Alkaline serum phosphatase was 45·6 units (normal 10 to 20). Takata-Ara reaction was negative.

In view of the obstructive type of jaundice, with a high serum phosphatase and no anaemia, atresia of the bile duct was suspected and reassessment of the case in a further fortnight decided upon. Meanwhile the baby was sent home. More than a week later he was readmitted in extreme dehydration following five days' diarrhoea and vomiting, and died after a few hours. Necropsy showed a wasted, jaundiced infant with moderately enlarged liver and a gall-bladder of normal size. Bile could be squeezed through the common bile duct. Four small dark pigment stones were found in the common bile duct and cystic duct, together with much pigment-sand which was also present in the gall-bladder. There was some dilatation of the bile passages, including the hepatic ducts behind the site of partial obstruction (fig. 1). The portal systems were enlarged, with a moderate increase of reticulin which was dense and stained with van Gieson's mixture (figs. 2 and 3). There was some albuminous degeneration of liver cells. The sinusoids were congested; the bile duct epithelium was normal. An occasional bile thrombus was seen in the intercellular bile canaliculi.

COMMENT. This is a case of erythroblastosis foetalis due to Rh iso-immunization, coming to necropsy during an obstructive phase of jaundice. The obstruction was extrahepatic in nature, due to the presence of bile pigment stones within the larger bile ducts, the liver being comparatively normal. We are not aware of any previous reports of such nature in proved cases of Rh incompatibility, and the tendency to formation of bile pigment stones in this neonatal form of haemolytic jaundice has not received attention.

Pigment stones were also found in another similar case. An infant, aged six months, with a history of jaundice lasting from the second day for five weeks. At six months of age there was no anaemia. The baby was Rh-positive, the mother Rh-negative, with a Rh antibody, titre 1 in 64. The liver was one finger's breadth below the costal margin. The spleen was not palpable. At necropsy the liver was macroscopically and microscopically normal. The gall-bladder was small and contained pale bile and three small pigment stones. The bile passages were patent.

Still (1927) reported three cases of biliary calculi in infants aged nine months, eight months, and five months respectively, with no history of jaundice in any of them. At the same time he reviewed some twenty cases reported in the literature, and some of these were infants with jaundice, and may have been associated with icterus gravis neonatorum.

In the literature of icterus gravis there are reports referring to obstructive jaundice in newly-born infants being due to inspissated bile within the larger bile ducts (Skelton and Tovey, 1945; Davidsohn, 1945; Ladd, 1935). Moreover, in certain instances surgeons have claimed to have dislodged the obstructing masses by manipulation, but could hardly have been sure of their nature; therefore the tendency to formation of bile-pigment stones in this type of haemolytic disease, as in acholuric jaundice, is of interest. Perhaps after a phase of intrahepatic obstruction with bile plugs within the finer branches of the bile ducts, these plugs become dislodged and pass into the larger bile ducts and form concretions there. Such a mechanism may be responsible in certain cases of prolonged obstructive jaundice in association with erythroblastosis foetalis. There is, however, another mechanism.

B. Cirrhosis causing Intrahepatic Obstruction

Case 4. G. B., a female, aged seven weeks, came under the care of Dr. Donald Paterson at the Hospital for Sick Children, Great Ormond Street, London. This was a third child, one having had erythroblastosis and being alive and well, and one having died from erythroblastosis and pneumonia. The patient had jaundice from birth, and was Rh-positive; the mother was Rh-negative, with Rh antibody, titre 1 in 8; the father was homozygous Rh_1Rh_1. An Rh-negative blood transfusion, 120 c.cm., was given when the child was four days old. Haemoglobin was 98 per cent. before transfusion and dropped to 66 per cent. at 15 days. There was increasing abdominal swelling from the sixth week of life. When admitted to hospital, the child had a swollen abdomen and cyanosis. She was jaundiced, with faint heart sounds and fluid in the abdomen. Red blood cells were 3,540,000 per c.mm., no normoblasts. Yellowish fluid (150 c.cm.) was withdrawn, and subsequently an uneven liver palpated. Another Rh-negative blood transfusion of 70 c.cm. was given, but the infant died three days after admission.

At necropsy there was a good deal of clear yellow free fluid in the abdominal cavity. The liver was large, firm, and greenish-brown, the surface finely granular. Cross section suggested fibrosis. The liver showed marked fatty degeneration and disintegration of liver cells, with perilobular and multicellular cirrhosis. There were many bile thrombi within the intercellular canaliculi, normal bile duct epithelium, and no evidence of erythropoiesis (figs. 4 to 7).

COMMENT. This was a case of Rh iso-immunization with obstructive jaundice of seven weeks' standing, showing cirrhosis of the liver at necropsy with evidence of intrahepatic bile duct obstruction.

Case 5. M. C., a male full-term baby, weighing 7 lb. 14 oz. at birth, left the maternity department of a London hospital on the twelfth day, weighing 7 lb. 8 oz., with no abnormal physical signs. He was readmitted to the hospital at six weeks because he had not gained weight since birth. We could not obtain any history of neonatal jaundice from the mother, but the Rh serology was investigated. The baby was Rh-positive, the father homozygous Rh_1Rh_1, and the mother Rh-negative, with weak anti-Rh agglutinins in serum, titre 1 in 1—but none were present in her milk. At eleven weeks the baby was noticed to be very pale, and a blood count gave the following results: red blood cells 2,540,000 per c.mm.; haemoglobin 46 per cent.; colour index 0·92. The weight was 9 lb. 10 oz. He was given an

FIG. 1.

FIG. 1—Liver, case 3, showing four pigment stones in dilated common bile duct and cystic duct. (Natural size.)

FIG. 2.—Microphotograph of liver, case 3, showing normal liver pattern and a large portal system with increase in collagen. Stained by van Gieson. (× 90.)

FIG. 3.—Microphotograph of liver, case 3, showing increase in reticulin in portal systems. Silver impregnation stain. (× 60.)

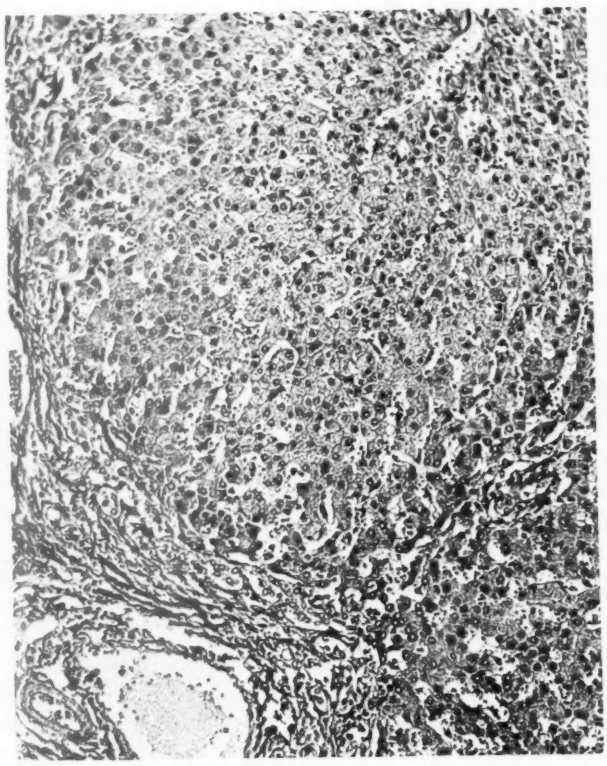

FIG. 2.

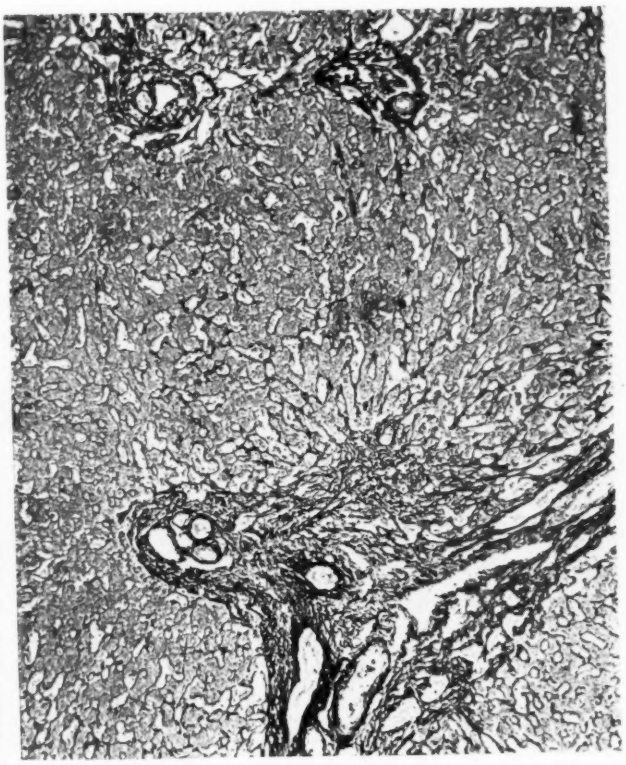

FIG. 3.

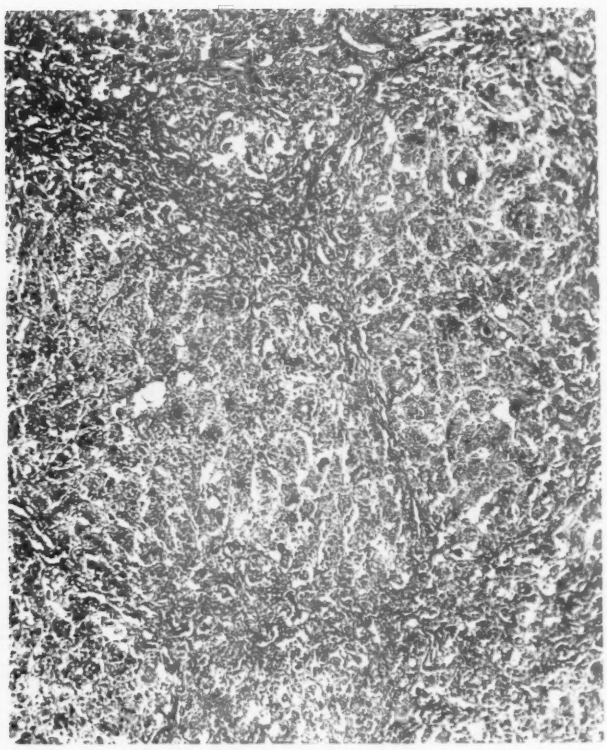

FIG. 4.—Microphotograph of liver, case 4, showing early perilobular cirrhosis and many intercellular bile thrombi. Stained by van Gieson. (× 60.)

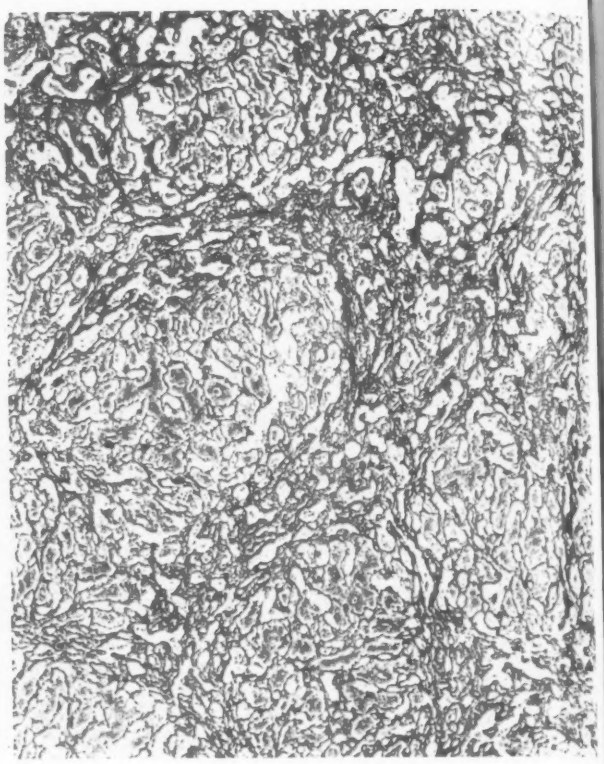

FIG. 5.—Microphotograph of liver, case 4, showing increase and condensation of reticulin, particularly in perilobular areas. Silver impregnation stain. (× 60.)

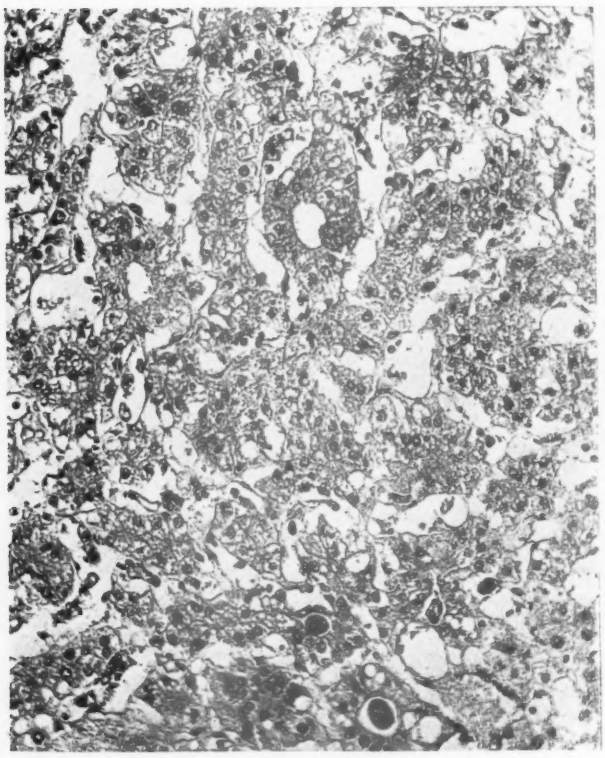

FIG. 6.—Microphotograph of liver, case 4, showing vacuolation (fatty degeneration) and necrosis of liver cells. Many intercellular bile thrombi are present. Stained by haematoxylin and eosin. (× 175.)

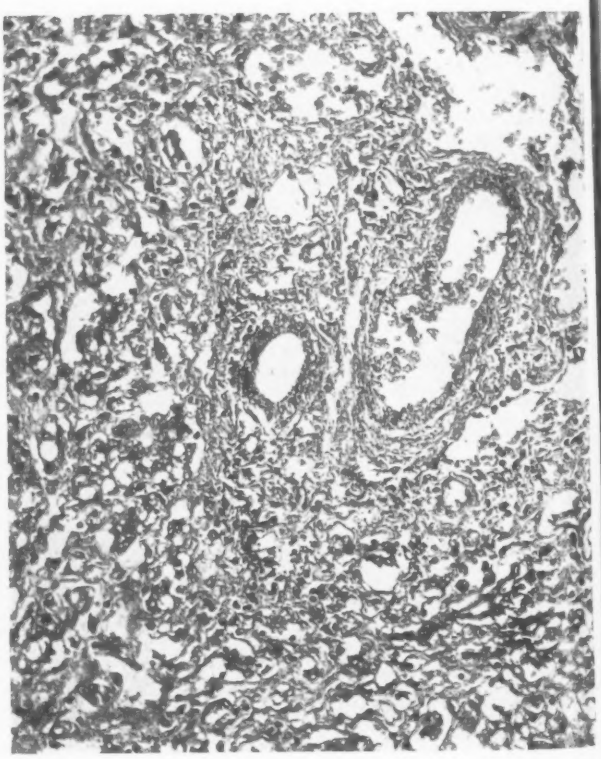

FIG. 7.—Microphotograph of liver, case 4, showing a bile duct with normal epithelium in a portal system, surrounded by disintegrated liver columns.

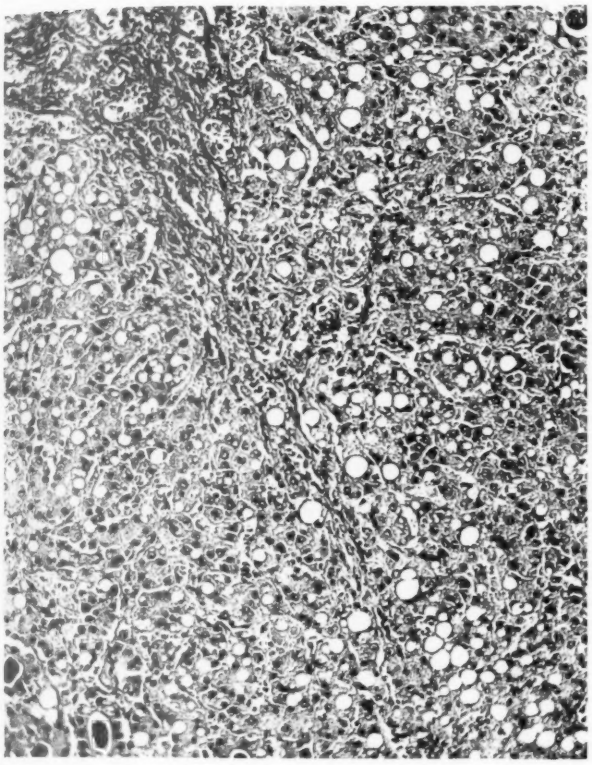

FIG. 8.—Microphotograph of liver, case 5, showing early portal and perilobular cirrhosis, marked vacuolation of liver cells (fatty degeneration), and a number of intercellular bile thrombi. Stained by van Gieson. (× 112.)

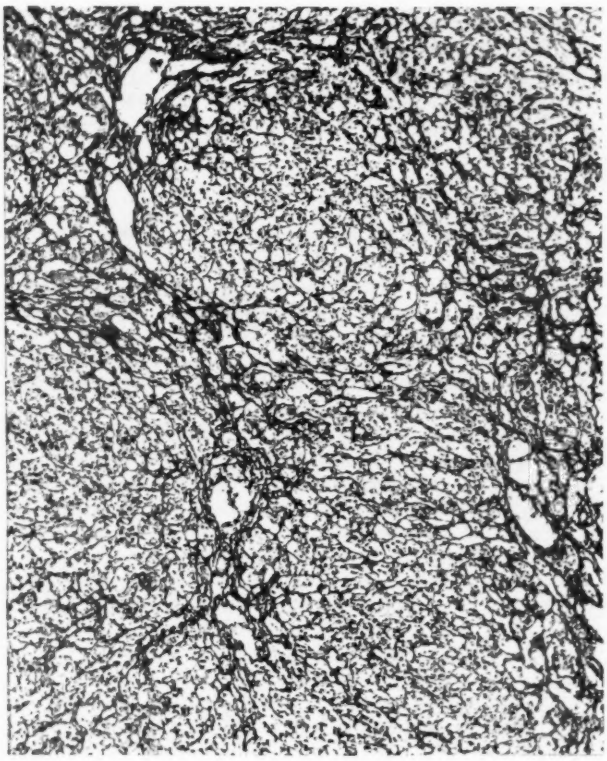

FIG. 9.—Microphotograph of liver, case 5, showing increase and condensation of reticulin in portal systems and perilobular areas. Silver impregnation stain. (× 60.)

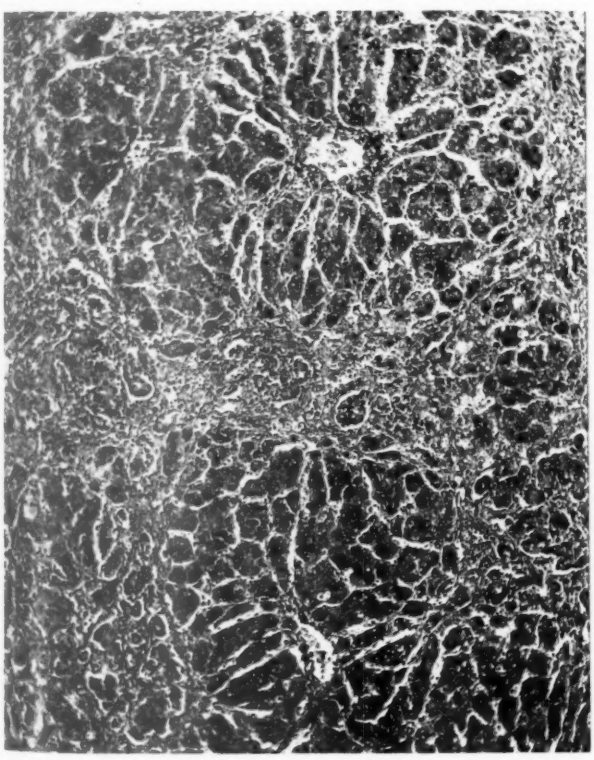

FIG. 10.—Microphotograph of liver, sibling of case 5, showing fibrous bands with round cell infiltration, surrounding large and small groups of liver cells. Stained by van Gieson. (× 60.)

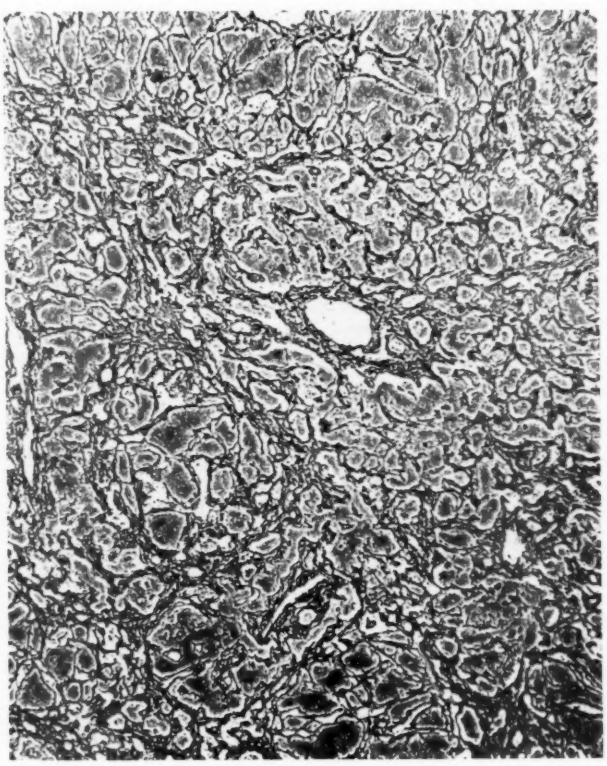

FIG. 11.—Microphotograph of liver, sibling of case 5, showing increase and condensation of reticulin fibres breaking up liver columns into large and small cell groups. Silver impregnation stain. (× 60.)

iron mixture and did not attend the hospital for about six weeks. At five and a half months he was admitted to the Hospital for Sick Children, Great Ormond Street, under Dr. B. Schlesinger. He was considerably under weight, the liver was firm and enlarged two fingers' breadth below the costal margin. The spleen was not palpable, and there was no jaundice or oedema. Rh investigations of the former hospital were confirmed. Red blood cells were 4,650,000 per c.mm., and the serum, van den Bergh, and Takata-Ara reactions were negative. Alkaline serum phosphatase was 24·9 units (normal 10 to 20 units). The blood Wassermann reaction was negative.

Three weeks after admission the baby developed a severe middle-ear infection, with diarrhoea and vomiting, jaundice, teleangiectases, and small haematemeses, and he died. At necropsy the liver was three fingers' breadth below the costal margin, firm, with finely granular surface. The gall-bladder was normal. The bile passages were patent throughout. Histology of the liver showed early fibrosis, perilobular, and also round small cell groups. There was marked vacuolation of liver cells. The bile duct epithelium was normal. A fair number of bile plugs were found in the intercellular bile canaliculi, and small bile globules in liver cells (figs. 8, 9).

COMMENT. This case of Rh iso-immunization is of interest because at a late stage considerable anaemia developed. Jaundice was not discovered in the early stages. At necropsy, cirrhosis of the liver was found. Another point of interest is the family history, and this is the main reason why the case is included in our series. Siblings were as follows: (1) a miscarriage in 1934; (2) a male child died at three months of ? marasmus in 1935 (? history of dropsy, no further details available); (3) a baby, born in 1939, died at ten weeks of cirrhosis of the liver; (4) the fourth child was the baby whose case is described above.

HISTORY OF THE THIRD CHILD

The third child of this family, a female, was jaundiced from the third day for a short time. At seven weeks an obstructive phase of jaundice developed and lasted eight days. A third phase of jaundice developed at nine weeks, with diarrhoea and blood-stained stools, and the infant was admitted to the Hospital for Sick Children, Great Ormond Street, London. Red blood cells were 2,960,000 per c.mm., haemoglobin 60 per cent., blood Wassermann reaction negative. A laparotomy was performed, and a large quantity of free fluid removed. The liver was small and greenish-yellow, and the gall-bladder dilated. The bile ducts were apparently normal. Two days later the operation findings were confirmed at necropsy. Histology of the liver showed intense multicellular fibrosis with numerous intercellular bile thrombi. The epithelium of the bile ducts was normal.

This baby must have been Rh-positive, since her father was homozygous Rh-positive. No test was made for Rh agglutinins in the mother's serum (in 1939) but it is reasonable to assume that the third infant was a case of Rh iso-immunization, as was the fourth child (case 5 above), and that this led to liver cirrhosis in both cases. The intermittent obstructive jaundice is another interesting feature in this case.

Discussion

The fundamental work on iso-immunization in erythroblastosis has taken us far on the road to full understanding of this disease, but understanding will not be complete until a number of clinical and pathological facts have been correlated. For instance, why should the clinical symptoms occasionally make their first appearance as late as the third or fourth week after birth? Why should the jaundice sometimes persist for several weeks or even months? In erythroblastosis the haematology has been intensively studied, but the pathology of the liver has received insufficient attention; haemopoiesis has been generally noted, but little attention has been given to the changes which can often be seen in the liver cells. In early cases of icterus gravis, Hawksley and Lightwood (1934) showed the possibility of considerable necrosis in the polygonal cells, and that hepatic cirrhosis may follow at a later stage. These observations were confirmed by Henderson (1942), who found even greater changes in stillborn erythroblastic foetuses, and by Gilmour (1944).

The condition of the bile ducts in erythroblastosis has also received too little attention. On clinical grounds the jaundice has been regarded as purely haemolytic. In icterus gravis the stools are usually well-coloured and bile pigment is often excessive. Hawksley and Lightwood (1934) accepted the haemolytic mechanism, but showed that there could be an evanescent obstructive phase as well. Thus it became necessary to recognize two mechanisms, haemolytic and obstructive (Ross and Waugh, 1936), and haemolysis is the factor chiefly concerned.

Biliary obstruction may occur at the height of the haemolytic jaundice or may only appear two to four weeks afterwards. The icterus is never wholly obstructive unless a late stage is reached. It is when the phase of obstruction is prolonged that confusion with congenital obliteration of the bile ducts is likely (Lightwood, 1943). Both conditions may show clinical remissions. Anaemia is often present in cases of atresia of the bile ducts, and we have seen counts of 3,000,000 red cells per c.mm.; in one case (M. S., see p. 2) the red count was 1,500,000 per c.mm. The presence or absence of bile in urine and stools are certainly not distinguishing features: we have seen cases of icterus gravis in which stercobilin was absent from stools. The alkaline serum phosphatase may be of critical value. A normal value is evidence against extrahepatic obstruction. The degree of rise in phosphatase does not, however, help in differentiating intrahepatic from extrahepatic obstruction: we have seen values of some 40 units in atresia of the bile ducts, and of some 80 units in cirrhosis of the liver with patent main bile ducts. On the other hand, low values may be found in cirrhosis and higher figures in atresia.

The data in the present paper suggest that biliary obstruction may appear as early as the first week in cases of erythroblastosis, or later, and that, once established, this type of icterus may continue for several months, or pursue a recurrent course.

In our fatal cases we have observed varying

degrees of albuminous degeneration, fatty degeneration, and focal or diffuse necrosis of liver cells. Increase of reticulin was noted in all the fatal cases. In some it was most marked in the portal systems, which were enlarged. In other cases reticulin was particularly increased in the periphery of the lobules, but also around small groups of cells. Where reticulin fibrils were condensed, they could be stained with van Gieson's mixture. We have deliberately looked for histological evidence to indicate that the lining epithelium of the bile ducts can be damaged or structurally altered in icterus gravis, for example by an antigen-antibody reaction in the neighbourhood, or by stagnation of bile in their lumina. No such evidence has been seen. In a few cases we have found that the obstruction is extrahepatic through the presence of pigment stones in the larger ducts.

In icterus gravis, where there is prolonged biliary obstruction, the clinical picture closely resembles congenital atresia, and it is natural that a causal relation has been suggested by more than one observer, but we have been unable to obtain any wholly satisfactory evidence of any such cause and effect. Although there are records of suggestive cases, we find that the evidence to date does not indicate a true association.

While an obstructive jaundice persists, the prognosis remains in doubt though it is by no means necessarily bad. In favourable cases the jaundice eventually clears, but in others cirrhosis occurs.

Our findings in case 5 and sibling suggest another etiological factor for familial cirrhosis of the liver.

Summary

The first part of the paper contains a review of the literature of cases of biliary atresia thought to be causally associated with icterus gravis neonatorum. In the light of Rh serology, no such association appears to have been proved beyond doubt, though some cases are highly suggestive. At any rate, Rh iso-immunization would not appear to be a major etiological factor in the pathogenesis of atresia of bile ducts.

In the second part of the paper, specimen cases are reported illustrating the intermittent and the continuous obstructive type of jaundice occurring in icterus gravis. This is followed by case and necropsy reports indicating the pathology underlying obstructive jaundice in icterus gravis: intrahepatic obstruction due to liver-cell damage which may lead to cirrhosis of liver, or extrahepatic obstruction due to pigment stones in the main bile ducts. The diagnosis between these two conditions and atresia of the bile ducts is discussed.

We wish to acknowledge the kindness of those at the Hospital for Sick Children, Great Ormond Street, who have helped in the investigations of the material published in this paper, in particular of Mr. V. C. Conlay, A.I.M.L.T., who has been responsible for the histological preparations. We are also indebted to Mr. E. V. Willmott, A.R.P.S., for the microphotographs.

References

Davidsohn, I. (1945). *J. Amer. med. Ass.*, **127**, 633.
Gilmour, J. R. (1944). *Arch. Dis. Childh.*, **19**, 1.
Hawksley, J. C., and Lightwood, R. (1934). *Quart. J. Med.* N.S., **3**, 155.
Henderson, J. L. (1942). *Arch. Dis. Childh.*, **17**, 49.
Ladd, W. E. (1935). *Ann. Surg.*, **102**, 742.
Lightwood, R. (1943). *Arch. Dis. Childh.*, **18**, 156.
MacClure, E. (1931). *Z. Kinderheilk.*, **51**, 86.
Pasachoff, H.D. (1935). *Amer. J. Dis. Child.*, **50**, 1,084.
Ross, S. G. and Waugh, T. R. (1936). *Ibid.*, **51**, 1,059.
Sanford, H. N. (1940). *The New International Clinics*: Vol. 2. New series three; p. 159, and private communication.
Skelton, M. O., and Tovey, G. H. (1945). *Brit. med. J.*, **2**, 914.
Still, G. F. (1927). *Common Disorders and Diseases of Childhood*. 5th ed. Oxford University Press, p. 375. London.
—— (1899). *Trans. Path. Soc. Lond.*, **50**, 151.

THE ETIOLOGY OF INTERMITTENT OESOPHAGEAL REGURGITATION AND HAEMATEMESIS IN INFANTS

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Six infants of ages from one month to eighteen months have recently been examined by us because of apparently effortless intermittent vomiting which was often blood-stained. The symptoms they presented were fairly uniform. Vomiting or regurgitation, during or between feeds, dated from birth or soon afterwards; blood frequently appeared in the vomit—giving it a brown colour—or occurred in bright red patches or streaks. Between bouts the infant was cheerful and contented, but in periods of regurgitations was apathetic, sometimes looked strained, and might give a sharp cry before a vomit as if in pain. Gain in weight was slow and irregular, and some degree of anaemia was present. Occult blood could often be detected in the stools.

Review of the literature. We believe that these symptoms in infants have too often been attributed to bleeding peptic ulcers of the duodenum or stomach itself. Meiselas and Russakoff (1944), reviewing the literature, have drawn attention to the common finding of duodenal ulcer at autopsy in marasmic infants. Holt (1913) recorded 65 duodenal cases, of which the ages in 70 per cent. were between six months and fifteen months of age; the age incidence corresponding to the commonest period for marasmus. Of 64 infants with proved duodenal ulcers, 28 had blood in the stools, only 10 had bloody vomitus, and 6 had both. Bird, Limper, and Mayer (1941) give a ratio of two duodenal and pyloric to one gastric ulcer in the period from birth to fourteen days, and five to one between fifteen days and one year. They state that in the neonatal group the onset of symptoms is sudden and the ulcers bleed severely or perforate, while in the later age-group abdominal pain, vomiting—sometimes streaked with blood—and melaena occur for weeks before the onset of graver symptoms. All these authors—except in the marasmic group, where an ulcer is found unexpectedly at autopsy—emphasize pylorospasm, projectile vomiting, and acute illness with serious complications (perforation) as common symptoms of duodenal and gastric ulcer in infants.

More tardily, and chiefly by radiographic help, it has been recognized that vomiting—or rather regurgitation of coffee-grounds or bright red blood—may occur either in the presence of oesophagitis, or of a peptic ulcer at the lower end of the oesophagus in cases of congenital short oesophagus with partial thoracic stomach. Oesophageal ulcer has been reported nearly always in adults, rarely in children. In 1929, Hurst and Stewart collected twelve cases of oesophageal peptic ulcer, and in the same year Chevalier Jackson remarked on thirty-one active ulcers and sixty-seven scars of healed ulcers in 4,000 endoscopies, all apparently in adults. Since 1933, Dick and Hurst (1942) saw sixteen fresh cases of peptic ulcer of the oesophagus in association with congenital shortness of the oesophagus; but the four males in their series were between twenty-two and seventy-two years of age at the onset of symptoms, and the twelve females between eighteen and twenty-six years. The delay in onset of symptoms with such a congenital condition as short oesophagus and partial thoracic stomach is difficult to account for. The abnormality, however, has been found at autopsy in a man of 77 years who had no symptoms during life. An entirely thoracic stomach can be present without symptoms (personal communication by Dr. W. E. Snell of a case discovered accidentally by x rays); yet its presence in an infant with inability to retain any of its feeds because of regurgitation brought about its death at twelve weeks (fig. 1). Apparently, therefore, symptoms due to congenitally short oesophagus with partial thoracic stomach can have their onset at any age, though, according to the records available up to date, more commonly in adult life than childhood.

In 1930, Kelly, and in 1931, Findlay and Kelly described nine cases of congenitally short oesophagus with partial thoracic stomach in children, seven boys and two girls, with ages from four weeks to nine years and ten months. In these cases there was apparent congenital stenosis of the oesophagus, in eight of which the food passage below the narrowing was proved by endoscopy to be part of the stomach. In 1933, Jacob, Tweedie and Negus described the case of an infant of one year and seven months who suffered from vomiting on and off since birth. An x ray with barium suggested an oesophageal stricture opposite the sixth to eighth thoracic vertebrae, and endoscopy proved that the distal portion was part of the stomach. Haroen and Gerlings (1934), reported a case of a child who had vomited blood-stained material intermittently since she was a week old. Endoscopy revealed a short oesophagus with an ulcer at its lower end and a partial thoracic stomach. Dunhill's case (1935) was in an infant of eleven months, who had repeated vomiting tinged with blood during or twenty minutes

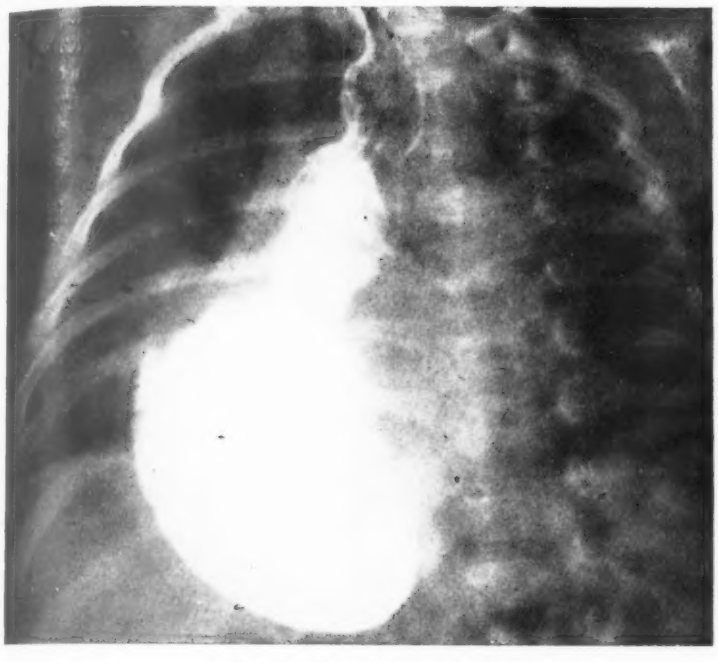

FIG. 1.—Thoracic stomach.

or so after a feed, with intervals of freedom up to fifteen days. With x rays and barium, gastric striae could be recognized in the supra-diaphragmatic portion of the stomach. On oesophagoscopy, an ulcer was seen in the lower end of the true oesophagus. Two other similar cases in early infancy were described, in 1940 by Lelong, Lamy, and Aimé, and in 1941 by Lesné, Rouget, and Longeaux. The interesting observation in these two reports was the absence of an associated constriction at the cardio-oesophageal juncture.

Most of the other reported cases, in infants as well as at later ages, have given on barium x-ray examination an appearance of one or two strictures. Oesophagoscopy shows the upper constriction to be just above the ulcer in the lower part of the oesophagus, a second contracture occurring below the ulcer at the oesophageo-gastric junction. The narrowings may in some cases be genuine stenosis, as it is not always possible to get the endoscope beyond the upper narrowing in order to see the ulcer; but the element of spasm immediately above the ulcer is important, and may simulate or exaggerate a stenosis. In radiographs of different dates the variations of degree of narrowing are often striking. Evidence of longitudinal striation seen above the level of the diaphragm in a barium x-ray is strongly in favour of an intrathoracic portion of the stomach.

In one of our six cases a stricture was present, but in the other five no narrowing was found. In one case the transition between oesophageal and gastric mucosa was seen by endoscopy (case 2) to be well above the diaphragm, thus indicating a short oesophagus. In three others no exact cardio-oesophageal demarcation was observed, but instead a gradual transition from a normal to a reddened swollen haemorrhagic mucosa. A possible explanation of the presence or absence of a constriction is that an ulcer is usually accompanied by spasm or stenosis on its proximal side, while an oesophagitis with haemorrhage can occur without spasm. It appears to have been this latter condition which was present in five of our cases.

Symptomatology. In adults the symptoms of peptic ulcer of the oesophagus, according to Hurst, are smarting or burning pain behind the sternum—sometimes heart-burn—felt while eating or drinking. The pain can be brought on by bending forward or lying down. In cases reported in infants and young children by Haroen and Gerlings, by Findlay and Kelly, and in our own cases, the symptoms noted were frequent spells of vomiting or regurgitation, often stained brown or red with blood, these occurring more often during a meal than later, and beginning from or soon after birth, or at the time of introduction to solid foods; the facial expression of the child, or a cry before regurgitation may suggest pain. The return of food seems to occur especially during recumbency—the commonest position of the infant—but even to some extent when being fed. The reason for this will be referred to later. Nutrition is usually poor, and anaemia present. In older children dysphagia is obvious; and Kelly, in cases with constriction of the oesophagus, mentions prolonged mastication and slow swallowing.

In the present series, screening of an infant during a barium swallow indicated the need for a more thorough investigation of all our cases and for making control observations on normal infants of the same age. In the latter the barium swallow normally descended in spindle-shaped boluses, which hesitated momentarily about the level of the diaphragm, entered the stomach, and did not return when the infant was placed in the supine position, even when pressure was exerted over the abdominal wall. On screening the affected infants in the supine position, however, the barium descended readily in most cases, but regurgitated with ease from stomach to oesophagus on inspiration, this probably being due to negative intrathoracic pressure which facilitated reopening of the oesophageal lumen. Manual pressure upon the abdomen during the procedure caused the re-entry of barium into the oesophagus to be greatly increased, even to the extent of its regurgitation into the mouth. There was evidently some incompetence at the cardia, or of the normal gastro-oesophageal valvular mechanism, which thus permitted a ready reflux of gastric contents.

Pathogenesis. Normally the oesophagus provides a one-way passage from mouth to stomach. Except

in belching or vomiting, in which the diaphragm, stomach, and cardia obey a special pattern of nervous stimuli, air and food are not rejected from stomach to mouth. The normal mechanism of closure between oesophagus and stomach still is a subject of debate. Yet its adequacy is such that water can be drunk and retained with the head dependent or even with the subject standing on his head. Prevention of regurgitation is essential to avoid loss of ingested food and also to secure the mucosa of the lower end of the oesophagus against peptic digestion.

The theories of closure at the cardia, which possibly are not exclusive, are as follows. Chevalier Jackson attributed closure to a diaphragmatic *pinchcock* or hiatal narrowing, depending on special bundles of muscle of the diaphragmatic crura extending round the oesophagus at its lower end, and contributing to its closure, or co-ordinate opening during deglutition. In addition he stressed the fact that below the diaphragm the oesophagus takes a leftward inclination at an angle of fifty degrees. The diaphragmatic pillars exert a downward milking contraction during inspiration. He did not consider that a special cardiac sphincter existed in the oesophageal musculature. Negus states that evidence of a sphincter is absent in cases of short oesophagus with thoracic stomach. He rightly draws attention to the difference of pressure normally acting in the thoracic and abdominal portions of the oesophagus. There is reduced pressure within the thorax, especially during inspiration, thus permitting easier opening of the oesophagus; while in the abdomen the pressure is raised, facilitating closure of the abdominal oesophagus by apposition of the viscera, due to descent of the diaphragm and contraction of the crura with narrowing of the hiatus.

Hurst upheld the existence of an oesophageal sphincter somewhere in the cardiac antrum, i.e. between the hiatus and the junction with the stomach. Knight, by excision of the sympathetic fibres surrounding the coeliac axis and left gastric arteries in cats, caused the cardiac sphincter to become patulous, allowing regurgitation of gastric contents into the oesophagus. Lendrum, in 150 autopsy specimens at all ages from foetal to senility, could find no evidence of a circular band of muscle resembling a sphincter at the cardia. Yet in the study of cardiospasm he agreed with Hurst that disturbance of the myenteric vagal plexus (Auerbach) permitted the sympathetic fibres to the terminal portion of the oesophagus to act unopposed, causing want of the normal relaxation during the act of swallowing. It is also stated that achalasia at the cardia can occur when the cardia is situated within the thorax, producing a much greater degree of oesophageal dilatation than would occur with stenosis (Dunhill). Lendrum's anatomical studies demonstrated that at the cardiac orifice the left margin of the oesophagus continues into the greater curvature of the stomach, or its fundus, at an acute angle—the incisura cardiaca; the right margin of the oesophagus is continuous in a gentle curve with the lesser curvature of the stomach. The acute angle formed by the left margin of the oesophagus and the junction of the greater curvature forms a valve-like structure which readily allows substances to enter the stomach, but prevents regurgitation by apposition closure, by the result of direct pressure from the presence of air in the fundus of the stomach, and by the relatively greater intra-abdominal pressure. The mechanical valve-like method of closure is naturally inoperative or non-existent when the oesophagus is short and continuous in a straight line with the part of the stomach which is intrathoracic (fig. 2).

The regurgitation of acid gastric contents into the lower part of the oesophagus can give rise to (1) oesophagitis, and (2) ulceration. By ligation of the pylorus in rats, Selye was able to produce peptic haemorrhagic changes in the lower thoracic part of the oesophagus as a result of regurgitation of the acid gastric juice. In oesophagitis, numerous angry red rugae which bleed easily are visible at endoscopy, but an ulcer shows clear-cut margins and may vary greatly in size. Bartels' study of autopsy material at the Mayo Clinic suggests that oesophagitis can also occur in debilitated subjects in which the oesophagus is of normal length. He found ulcerative oesophagitis in 82 of 6,000 consecutive post-mortem examinations. The ages in the affected cases were between eight and seventy-eight years. In fifty-four cases the condition had followed upon an operation. A tendency to hyperacidity has been mentioned as a determining factor at all ages, in the occurrence of oesophagitis, or of ulceration in cases of short oesophagus, but it was not the controlling factor of the vomiting in our infantile cases, where a simple mechanical fault—a lax cardia or cardiac incompetence—appeared to be the chief cause. Another cause of bleeding or ulceration often mentioned is islands of ectopic gastric mucosa at the lower end of the oesophagus. There is no doubt that these frequently exist, but their importance seems much exaggerated.

It is incorrect to speak of hiatal hernia of part of

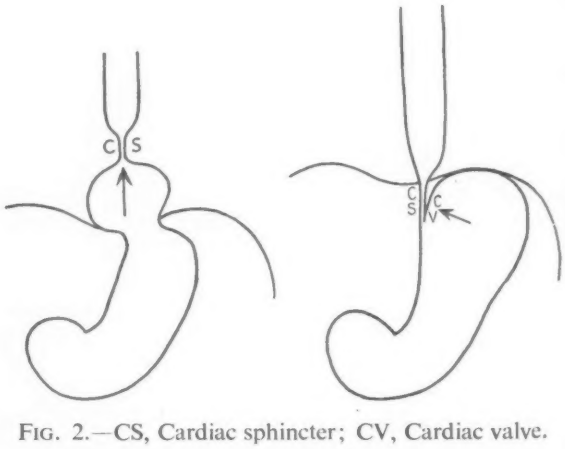

FIG. 2.—CS, Cardiac sphincter; CV, Cardiac valve.

From Dick and Hurst (1942). By kind permission of the *Quarterly Journal of Medicine*.

the stomach in cases of short oesophagus, as the want of development of the latter has prevented the normal complete descent of the stomach

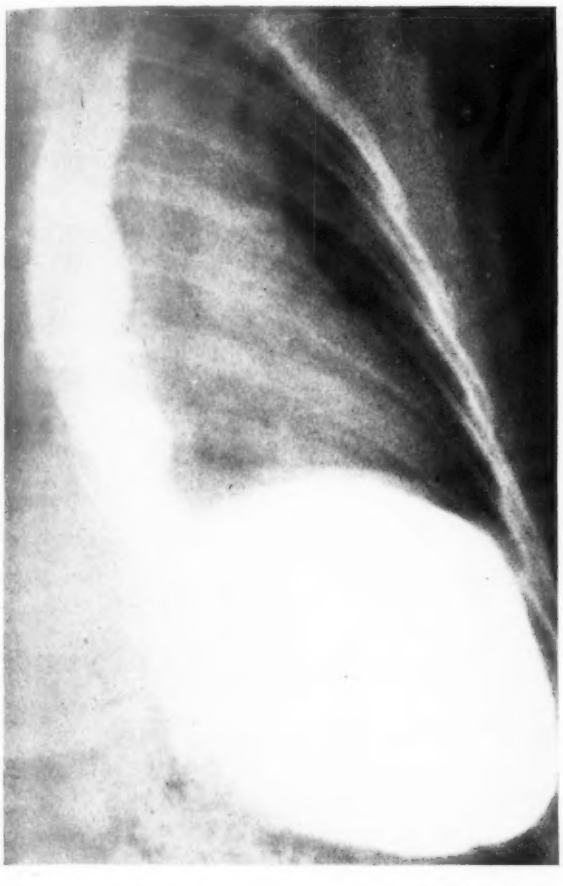

FIG. 3.—Barium swallow in case 1 (Trendelenburg position).

to below the diaphragm. The hiatus itself may be wider than normal, but is sufficiently competent to prevent any of the abdominal viscera being herniated into the thorax.

Case Histories

Case 1. A.B. was first seen at the age of one and a half years, when he weighed 19 lb. He had vomited periodically since birth, and on several occasions there had been visible blood in varying amounts, although 'brown mucus' had been vomited as early as nine weeks of age. At one year and two months a stool tested for occult blood was positive. He was born one month prematurely, his birth weight being 6 lb. 12 oz., and was breast fed for three months. Apart from an attack of pneumonia he had had no previous illnesses. The parents and five other children were all well.

FINDINGS. There was no apparent wasting, but the child was 4 lb. underweight. Otherwise he was physically and mentally normal for his age. He vomited about once a day—brown-flecked material which had no particular relation to food. The benzidine test for blood was strongly positive for the vomit, but negative for the stool. The blood haemoglobin was 96 per cent.

Barium meal. The barium emptied satisfactorily into the stomach, but when the child was placed in the supine position the barium flowed back easily into the oesophagus, which appeared to be dilated and to lack the usual smooth outline (fig. 3). There appeared to be no tone in the cardia or oesophagus as, on deep inspiration, the latter dilated up to a diameter of 4 cm. There was good emptying of the stomach in three hours, and no delay in the intestines.

Fractional test meal. This was normal, the total acids rising to 30 c.cm. after three quarters of an hour and falling to 10 c.cm. at the end of the hour. The free acid never rose above 10 c.cm.

Oesophagoscopy. Performed by Professor R. S. Pilcher. Showed the upper part of the oesophagus to be fairly normal, with gradual transition to a thick reddened mucosa with deep rugae. It was impossible to locate the exact position of the cardia or commencement of the stomach, as no constriction was seen. The oesophagus appeared to be dilated and atonic, and the mucus membrane bled easily although no actual ulcer crater was seen.

TREATMENT. Solid food, avoiding excess of liquids, was tried, and the child was propped up after a meal for two or three hours. There was slight improvement in the vomiting but no gain in weight over a period of two months.

Case 2. C.D., aged one year and three months, weight 19 lb. 1½ oz., had been vomiting intermittently since three days old; the vomit was often streaked with blood. He was born three weeks prematurely after a long labour, birth weight 7¼ lb. He was breast fed for six weeks.

FINDINGS. The infant was three pounds underweight and looked poorly nourished. He appeared reluctant to swallow, and vomited once or twice a day, although there were periods of several days with no vomiting. Visible blood was often present in the vomit, and the stool gave a positive benzidine reaction. Blood haemoglobin was 67 per cent. Bleeding time (modification of Duke's method) 3 minutes 30 seconds, and clotting time (Dale and Laidlaw) 2 minutes 5 seconds.

Barium swallow and meal. At one year, two months. The report states that the barium was held up for a considerable time about the cardia, and that, when the test was repeated three weeks later, there was periodic hold-up at the cardia with considerable hold-up in the stomach after three hours. The x ray (fig. 4) shows a patent cardia and dilated oesophagus with irregular outline. When repeated in another two weeks there was no hold up at the cardia but a slight contraction one inch above it. There was a pyloric hold-up for three hours. At two years and three months, the child was screened by Dr. L. G. Blair. There was no obstruction to the passage of barium into the stomach, but it flowed freely back into the oesophagus when the child was in the supine position. An x ray taken at the time showed dilatation and irregularity along the whole length of the oesophagus, particularly the lower third. There was no constriction to denote the position of the cardia.

Oesophagoscopy. (Mr. J. Crooks.) The transition from oesophageal to gastric mucosa occurred at 20 cm. from the incisor teeth without any recognizable sphincter or constriction. This is 3 cm. short of the normal distance for age from incisors to cardia. An opaque bougie was passed to the

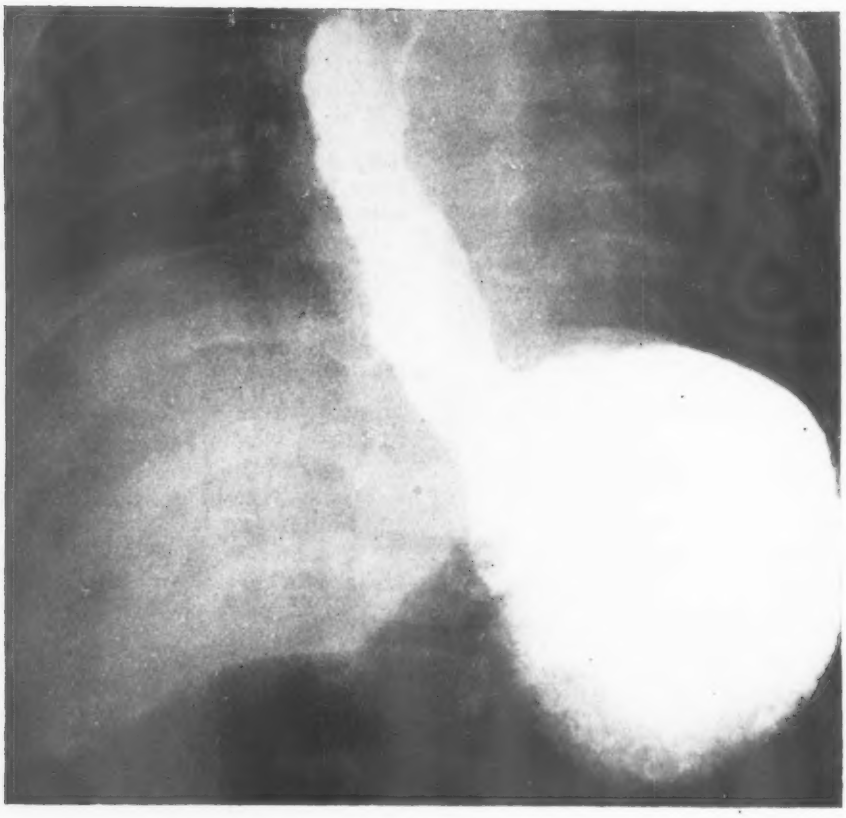

FIG. 4.—Barium swallow in case 2 (supine position).

site of mucosal transition, and an x ray proved this to be well above the diaphragm.

TREATMENT. Pylostropin (methylatropine nitrate), two lamellae before each feed, produced no alteration of the symptoms. Iron in the form of ferrous sulphate was given for the anaemia.

PROGRESS. Whilst at a convalescent home he developed chickenpox and pneumonia. During this time vomiting became more frequent, producing dehydration. He was finally discharged home ten months after admission to hospital. He was vomiting less, having gained five pounds in the ten months; blood haemoglobin was 78 per cent.

Case 3. E. G., aged eleven months, weight 13 lb. 15 oz., had vomited since birth. Although he took feeds well, he vomited during or after most feeds, and even after solids. His birth weight was 7 lb. 14 oz., and he was breast fed for nine months. He was the first baby, and parents were healthy; pregnancy and labour were normal.

FINDINGS. He was pale, hypotonic, and miserable, had two teeth, and could sit up. A few rhonchi were heard in the chest; otherwise there were no abnormal physical signs. Shortly after admission he developed bilateral otitis media which resolved after myringotomy. He vomited periodically whilst in hospital, sometimes as often as three or four times a day; then there might be no further vomiting for two or three days. The vomit frequently contained blood, and the stools showed a positive benzidine reaction. The blood haemoglobin was 69 per cent. and the leucocyte count 8,300 per c.mm.

Barium meal. This was done at the age of eleven months and one year, and showed no hold-up. Dr. L. G. Blair reports on a repeat meal at one year and ten months as follows: 'I could find no lesion in the stomach or duodenum. The child regurgitates food easily into the oesophagus, the lower end of which dilates rather easily.' When repeated again two weeks later, the oesophagus was observed to fill with barium from the stomach in the supine position, and on deep inspiration the oesophagus dilated up to 4 c.cm. in diameter.

Oesophagoscopy. Performed at one year, eleven months by Mr. J. Crooks. The oesophagoscope was passed for 23 cm. There was no constriction or difficulty encountered at the cardia on passing the instrument. The mucus membrane of the oesophagus and stomach was very red and bled easily, and that of the oesophagus showed numerous angry rugae.

PROGRESS. Intermittent vomiting, sometimes with blood, continued, but the child made satisfactory general progress and gained weight, being 22 lb. 10 oz. at one year, eleven months. The last blood count was quite normal. Haemoglobin 100 per cent. Leucocytes 11,200 per c.mm. of blood.

Case 4. H. J., weight 6 lb. 12 oz., first attended an infant welfare centre at the age of one month. The story was that he had vomited after practically every feed since birth. He was a full-term baby; delivery was normal, birth weight 7 lb. 6 oz. He was breast fed. Mother and father and one other child were healthy.

FINDINGS. There were no abnormal physical signs and the breast feeding was satisfactory.

PROGRESS. He continued to vomit, and this was sometimes streaked with brown or contained bright red clots of blood. Sometimes he screamed as if in pain. In spite of the vomiting he continued to gain weight. At five months of age he was weaned and admitted to hospital, now weighing 14 lb. 11 oz.

Barium swallow. Observed at one month and repeated at five months of age, showed no hold-up, but on reviewing the x rays three years later it was noticed that the pictures showed a dilated oesophagus filled with barium, and an open cardiac orifice (fig. 5). These findings were confirmed when a barium swallow was repeated at three years and nine months, and when he was lain down barium regurgitated with ease into the oesophagus, which appeared atonic and which dilated considerably on inspiration.

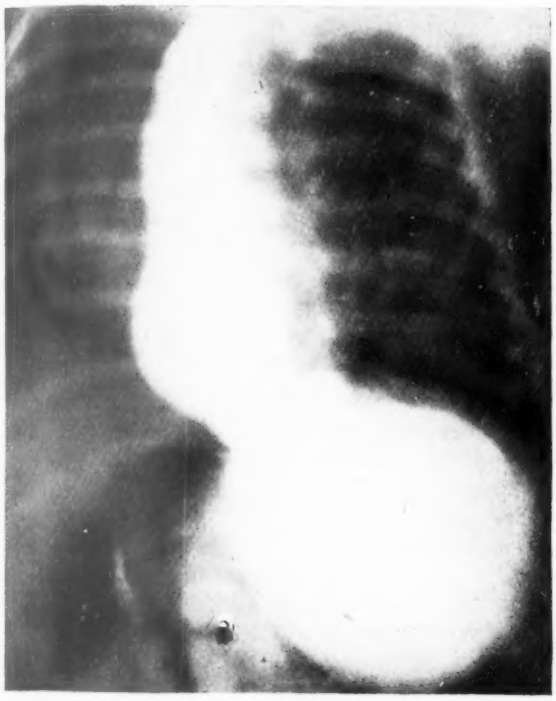

FIG. 5.—Barium swallow in case 4.

Barium meal. Taken at one month and repeated at five and at eleven months. Showed no difficulty in transit to stomach.

Fractional test meal. This was performed at five and at eleven months. There was no free HCl. Total acids were 25 c.cm. in the resting juice and fell to 10 c.cm. after a meal of gruel. Blood was present.

Stool. Benzidine test and spectroscopic examination strongly positive for blood.

Blood counts. These were repeated frequently, and only on one occasion was there a small reduction in the erythrocyte count.

Bleeding time. Three minutes fifteen seconds.

TREATMENT. Shortly after admission to hospital he developed loose stools, and, with the frequent vomiting, required intravenous therapy followed by 200 c.cm. of blood. He was then tried on eumydrin, 1 c.cm. of 1 in 10,000 solution before each feed, and vomiting ceased, returning when the drug was discontinued. Pylostropin, one lamella before each feed, was then tried, and again vomiting ceased. The pylostropin was finally discontinued after six weeks of treatment, the child having then about one small vomit a day.

FURTHER PROGRESS. The infant was finally discharged home from hospital at nine months of age, but returned in one week, vomiting again with streaks of blood, and once a teacupful of blood. Haemoglobin had dropped to 68 per cent. He was again treated with pylostropin and sent home. Vomiting slowly improved, but he began to have convulsions, with loss of consciousness, which have now been diagnosed as epilepsy. Vomiting finally ceased at a year old.

At three years, nine months the case was reviewed. There had been no further vomiting, but the epileptic fits continued. A barium swallow at this time has already been described.

Oesophagoscopy. At three years and nine months. Professor R. S. Pilcher reported: 'The upper part of the oesophagus was normal. At 25 cm. the respiratory movements were almost absent and the mucosa was folded longitudinally, the folds being in contact. The oesophagoscope passed through these folds for 3 cm., where the view was obscured by fluid—presumably gastric contents. The mucosa between 25 cm. and 28 cm. may be gastric, and I think the cardia was at about 28 cm. distance.'

Case 5. K. L. was admitted to hospital at the age of one year and two months, weight 12 lb. 12 oz. She was said to have been vomiting two or three times a day since five months old, usually immediately after food. Sometimes the vomits were flecked with blood or like thick chocolate. On one occasion stools were black. She was a premature baby, birth weight 4 lb. Delivery was normal, and she was breast fed for five months, but vomiting started before weaning. There were four other children, all premature; one died at eight days. Parents were healthy.

FINDINGS. She looked well and was a happy child and only once appeared to have pain.

Barium swallow. Showed no abnormality. The barium passed into the stomach without obstruction, but regurgitation was not particularly looked for.

Barium meal. On two occasions showed no abnormality and nothing to suggest gastric or duodenal ulceration.

Fractional test meal. Performed twice. On both occasions the free and total acid contents rose during the three hours The free HCl in the resting juice was 5 c.cm. on both occasions, rising to 35 c.cm. and 50 c.cm. respectively in three hours. The total acids were 10 c.cm. in the resting juice, rising to 50 c.cm. and 70 c.cm. in three hours. Blood was present in all specimens, but no bile.

Blood count. Erythrocytes 4,150,000 per c.mm. of blood. Haemoglobin 72 per cent. Colour index 0·86. Leucocytes 11,800 per c.mm. of blood, platelets 230,000 per c.mm.

Bleeding time. One minute thirty seconds (reported normal one to three minutes). Coagulation time four minutes (normal two to six minutes).

Oesophagoscopy. Not performed.

TREATMENT. A variety of treatments were tried, including a milk diet and alkalies as for an ulcer, also belladonna and olive oil, but the child continued

to vomit with periodic large haematemeses, and on one occasion this appeared to be preceded by pain.

PROGRESS. She was finally discharged home in a good phase, and owing to distance has not been seen since. But the mother writes stating that she continued to vomit until three and a half years of age. Periodically she would vomit chocolate-coloured material, and at these times her motions were black. The mother's last letter states that she is now five years and three months, weighs 2 st. 6 lb., and has had no further vomiting for the last year and a half.

Case 6. M. P. was admitted to hospital at one year old with the story that she had had dark vomits since birth, diminishing in frequency as she grew older. At feed times she became restless as if in pain, and this appeared to be relieved by vomiting. There was one other child in the family, and parents were healthy.

FINDINGS. She was a cheerful child with pale sallow complexion. She was thin, weighing only 15 lb. 9½ oz. She vomited repeatedly several times during a meal, and the vomit frequently contained blood.

Blood count. Erythrocytes 4,300,000 per c.mm. of blood. Haemoglobin 68 per cent. Colour index 0·79. Leucocytes 20,000 per c.mm. Platelets 180,000 per c.mm.

Bleeding time. Three minutes. Coagulation time, one minute thirty seconds.

Stool. Benzidine test and spectroscopic examination positive for blood.

Fractional test meal. At three years, two months, showed no free HCl in the resting juice, and only 10 c.cm. of total acids. Two and a half hours after the gruel the free HCl rose to 25 c.cm. and the total acid to 45 c.cm. Flecks of blood were present, but no bile.

Barium meal. At one year showed marked peristalsis of the stomach, but no hold-up at the pylorus; no ulcer crater was seen. It was repeated at three years, two months, and no abnormality was detected.

TREATMENT. No particular treatment was given, except iron for the anaemia.

PROGRESS. She was finally discharged home, but continued to have blood vomits and later complained of pain in her abdomen. She was re-admitted to hospital twice for these symptoms. She looked well, had no anaemia (haemoglobin 101 per cent.), but still continued to vomit occasionally. No blood was this time detected in the vomit.

Barium swallow. At three years, nine months. On first impression there appeared to be no hold-up to the barium, but closer observation revealed—at about 3 cm. from the cardia and 2¼ cm. from the diaphragm—a momentary hesitation to the passage of the barium, which then passed on into the stomach as a thin ribbon-like column. This finding was constant with each swallow. There was no definite dilatation of the oesophagus above, and no regurgitation of barium from the stomach.

Oesophagoscopy. Performed by Mr. J. Crooks. 'The oesophagoscope passed for 20 cm. from the teeth. The lower 4 cm. of oesophagus was stenosed to about the thickness of a pocket-book pencil and ulcerated, bleeding easily. The cardia was not seen.'

Treatment

An important factor in facilitating the vomiting in cases of incompetence of the cardia and short oesophagus is decubitus, notably in the supine position. As this is the normal posture for infants, it explains the ease with which acid gastric contents regurgitate. This was certainly so in the cases observed by us; but in the more numerous cases of short oesophagus reported with onset of symptoms in adult life, no history is provided of difficulties encountered during infantile feeding. We found the most satisfactory treatment was to raise the head of the cot on blocks, to prop the infant up on pillows to prevent regurgitations, and to give thickened feeds. A more upright position is automatically assumed as the age of weaning takes place, which may explain why in all our cases gradually the regurgitations became less. Without any other particular treatment these infants usually recover by two or three years of age. Drugs of the belladonna-atropine group produced little or no improvement.

Summary

Six cases of intermittent haematemesis in infants are reported. Case 2 was proved to be a congenital short oesophagus, and case 6 a stricture of the oesophagus.

It is suggested that the symptoms in cases 1, 3, 4 and 5 were due to a lax or incompetent cardia permitting regurgitation of gastric contents, thereby causing haemorrhagic oesophagitis.

Our thanks are due to Professor R. S. Pilcher and Mr. J. Crooks for the endoscopic examinations.

REFERENCES

Bartels, E. C. (1935). *Arch. Pathol.*, **20**, 369.
Bird, C. E., Limper, M. A., and Mayer, J. M. (1941). *Ann. Surg.*, **114**, 526.
Dick, R. C. S., and Hurst, A. (1942). *Quart. J. Med.*, **11**, 105.
Dunhill, T. (1935). *Brit. J. Surg.*, **22**, 475.
Findlay, L., and Kelly, A. B. (1931). *J. Laryng.*, **46**, 797.
Haroen, I. L., and Gerlings, P. G. (1934). *Acta Otolaryng., Stockh.*, **19**, 461.
Holt, L. E. (1913). *Amer. J. Dis. Child.*, **6**, 381.
Hurst, A. F., and Stewart, M. J. (1929). *Gastric and Duodenal Ulcer.* London.
Jackson, Chevalier (1922). *Laryngoscope*, **32**, 139.
Jacob, F. H., Tweedie, A., and Negus, V. E. (1933). *J. Laryng.*, **48**, 486.
Kelly, A. B. (1930). *Ibid.*, **45**, 680.
Knight, G. C. (1934). *Brit. J. Surg.*, **22**, 155.
Lelong, M., Lamy, M., and Aimé, P. (1940). *Bull. Mem. Soc. méd. Hôp., Paris*, **56**, 681.
Lendrum, F. C. (1937). *Arch. intern. Med.*, **59**, 474.
Lesné, M. E., Rouget, D., and Longeaux, S. (1941). *Bull. Mem. Soc. méd. Hôp., Paris*, **56**, 687.
Meiselas, L. E., and Russakoff, A. H. (1944). *Amer. J. Dis. Child.*, **67**, 384.
Negus, V. E. (1942). *Proc. roy. Soc. Med., Sect. Laryng.*, **36**, 85.
Selye, H. (1938). *Canad. med. Ass. J.*, **39**, 447.

OBSERVATIONS ON HAEMOLYTIC DISEASE OF THE NEWBORN*

BY

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This article deals briefly with three aspects of haemolytic disease of the newborn which are of special interest. The first is the family history, with special reference to the occurrence of stillbirths and abortions in previous pregnancies; the second is the correlation of clinical and serological findings; and the third is the mortality rate. The observations recorded are based on 119 cases of icterus gravis neonatorum which were admitted to the Royal Hospital for Sick Children, Glasgow, from January, 1934, to April, 1946. The one case of hydrops foetalis, and the twenty-five cases of congenital haemolytic anaemia which were also admitted during this period, are not included.

Family History

It has been known for many years that icterus gravis neonatorum is a familial disease. The fact that a previous child suffered from jaundice shortly after birth is of importance in the differential diagnosis of any case of neonatal jaundice. With the discovery of the Rhesus factor and the mechanism by which the disease can be produced, the exact reason for this has become apparent. It has been suggested that the antibodies in the maternal serum can be held responsible for abortions and stillbirths as well as for affected children. If this is so, a history of abortions and stillbirths would rank in importance with that of a previously jaundiced child. In an attempt to discover the value of such a history, the obstetric histories of the mothers has been analysed (table 1).

TABLE 1

THE INCIDENCE OF ABORTIONS AND STILLBIRTHS IN 112 AFFECTED FAMILIES

Pregnancies	Abortions	Stillbirths	Live births
463	15	28	428

$$\text{abortion rate} = \frac{\text{abortions}}{\text{pregnancies}} \times 100 = 3{\cdot}2 \text{ per cent.}$$

$$\text{stillbirth rate} = \frac{\text{stillbirths}}{\text{live births}} \times 100 = 6{\cdot}5 \text{ per cent.}$$

Of the 119 cases, seven were siblings of infants already included, so that only 112 families are represented. In these families there were recorded 463 pregnancies. Fifteen of these ended in abortion before the seventh month of gestation, twenty-eight ended in stillbirth (either premature or full term) and eight resulted in twins. There were, therefore, 428 live births.

The abortion rate, which is defined as the percentage of pregnancies ending in abortion, is, in this series, 3·2 per cent. Since abortions do not have to be registered there are no national figures for their incidence, but obstetric textbooks (Eden and Holland, 1937; Munro Kerr et al., 1933) quote figures as high as 20 per cent. of all pregnancies. In any event, 3 per cent. cannot be considered above the average and it would appear that abortions are not more common in families where one infant has had icterus gravis than they are in the general population.

The stillbirth rate is the proportion of stillbirths to live births expressed as a percentage. In this series the figure is 6·5 per cent. Stillbirths are registrable and, in 1943, the incidence in Glasgow was 3·6 per cent. (Report of Medical Officer of Health, 1943.) The stillbirth rate is, therefore, almost double the average in families where there has been an infant suffering from icterus gravis. It would appear, therefore, that a history of previous stillbirths is of some importance in indicating maternal sensitization to the Rhesus factor, but that a history of previous abortions is of none.

Clinical and Serological Findings

The second point to be considered is the correlation of clinical and serological findings. It is usually found that the mother is Rh-negative, the infant Rh-positive, and that the mother's serum contains anti-Rh agglutinins. In some cases where the clinical findings are not typical, the serological findings may be of considerable help. Thus, recently, two infants have been seen, both thought to be examples of severe physiological icterus since in neither did blood examination reveal signs of haemolysis nor was there any splenomegaly, hepatomegaly, or bile in the urine. In both cases, however, the mother was found to be Rh-negative and her serum contained anti-Rh agglutinins active

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against the child's red cells. The infants were kept under observation; they became anaemic, with splenomegaly and erythroblastaemia, and recovered after transfusion. It is, therefore, of importance to have the Rh testing done in all cases of jaundice occurring within the first few days of life. Indeed, if all mothers could have their blood tested during the last months of pregnancy it would be a step towards anticipating the occurrence of the disease.

When the mother and child are both Rh-positive, reconciliation with the clinical findings is more difficult. When the mother's serum contains agglutinins active against the infant's red cells it may be assumed, in most cases, that this is responsible for the disease. Most frequently this is due to an ABO group difference, but sometimes one of the rare anti-Rh agglutinins may be found. It is known that the former may be associated with the disease, and if the anti-Rh agglutinins can pass through the placenta there seems no reason to doubt that the α and β agglutinins may also sometimes pass. The rare anti-Rh antibodies which may be present are anti-Rh′ (anti-C), anti-Rh″ (anti-E) or anti-Hr′ (anti-c). Only one anti-Hr″ (anti-e) has been reported (Mourant, 1945), and the presence of anti-d has, so far, only been predicted (Race, 1944). When any of these are found, it is as conclusive serological evidence as finding anti-Rh_0 (anti-D). It sometimes happens, however, that mother and child are both Rh-positive and there are no agglutinins in the maternal serum. Of the 112 families, fifty-two have so far reported for Rh-testing. Of these, forty-nine had the standard incompatibility of mother Rh-negative and child or father (or both) Rh-positive. In thirty-six of these the mother had anti-Rh agglutinins in her serum: in the thirteen in whom they were not found it was more than two years since the birth of an affected child.

In the three families where mother and child were both Rh-positive there were no agglutinins in the maternal serum. Although in all three it was also some time since the birth of an affected child, there was something in the clinical history of each which raised the question of the accuracy of the diagnosis. In all three of the infants there were some of the typical findings of the disease, namely jaundice, anaemia, reticulocytosis, splenomegaly, hepatomegaly, and biluria. It was on the presence of these that the diagnosis was made.

The first child, however, was the result of a first pregnancy; the jaundice was not noticed by the parents until the fifteenth day, and both before and after admission to hospital there had been considerable melaena. On admission there was haematuria, and the reticulocyte count was only 1 per cent., although this rose later without further apparent haemorrhage. The spleen was never palpable in this case, but the haemoglobin level fell to 50 per cent., and there was bile and a considerable amount of pus in the urine. The child eventually recovered but is now hopelessly mentally deficient. There have been no further pregnancies in the family.

The second child was the result of a third pregnancy, the first two having ended in abortion at the third month. The first abnormality noticed by the parents was a suprasternal swelling, apparently a haematoma although there were no other haemorrhages. The child became jaundiced and pale on the third day; liver and spleen both became enlarged but the urine did not contain bile. The haemoglobin was 52 per cent. and there was erythroblastaemia. This child recovered but, later, developed a haemarthrosis of his knee when two years old and finally died at the age of four years from a subarachnoid haemorrhage. Two further children born to this family were perfectly normal and both Rh-positive.

The third child was the thirteenth in the family; none of the others had been affected. He became jaundiced at two days and had two convulsions before his admission on the fourth day. His spleen was enlarged to four fingers' breadth below the costal margin, and his haemoglobin was 45 per cent. The reticulocyte count was 10 per cent., and there was no erythroblastaemia. This child recovered after transfusion and is well. This last case fitted more closely into the clinical picture than the other two, but maternal antibodies were only looked for on one occasion.

From study of the first two cases, the impression is gained that there are other conditions which may simulate the disease entity of icterus gravis. For example, the following case showed many of the features of the disease but was found at autopsy not to be affected.

The infant was apparently quite normal at birth; he was the second child in the family. He remained well until aged five weeks when he became jaundiced and drowsy. When admitted at seven weeks of age he had an enlarged liver and spleen, a haemoglobin of 104 per cent., and no reticulocytosis. Bile was present in the motions, and a gross pyuria was discovered. The pyuria and the jaundice cleared, and, as this occurred, the child became pale and his haemoglobin fell to 65 per cent. At the same time the reticulocytes rose to 12 per cent., although there was no increase in the number of nucleated red cells in the blood films. If the age of the child be excluded the picture is very similar to icterus gravis of fairly mild degree but the mother, father, and both children were all Rh-negative and the mother had no agglutinins to the others' red cells nor to any other of known Rh type. This child died, and at necropsy a healing pyelonephritis was the only abnormality found. To what extent the pyelonephritis was responsible for the other findings it is difficult to say, but it is interesting that the first of the three infants already described also had pyuria which was discovered two days after the haemoglobin had fallen suddenly from 90 to 50 per cent.

Boorman, Dodd, and Mollison (1944) found only three out of one hundred mothers of affected children to be Rh-positive. In two of these there was an incompatible ABO grouping with the child's cells; in the third there was present what is now known as the anti-E antibody. The earlier papers on the

subject (Levine, 1941) gave 10 per cent. as the incidence of Rh-positive mothers, but the findings in the series recorded in the present communication appear to agree with the more recent figures.

Mortality Rate

The mortality rate for his own, and Rolleston's (1920), cases was given by Hampson (1929) as 80 per cent. With the introduction of blood transfusion in the treatment of the disease the mortality dropped appreciably (table 2). When Rh-negative blood was introduced, great hopes were entertained that practically all affected children could be saved. The original papers published seemed very encouraging (Gimson, 1943; Mollison, 1943), but Mollison, when commenting on seventeen recoveries out of seventeen transfused cases, gave warning that such figures might not always be expected since many of the transfused cases were only mildly affected. That such has proved to be correct is seen from table 2.

TABLE 2

MORTALITY RATE IN ICTERUS GRAVIS NEONATORUM

	Before Rh	After Rh
A. In 119 cases treated and untreated:		
Number of cases	70	49
Number of deaths	43	16
Mortality rate (per cent.)	61·4	32·7
B. In 105 transfused cases:		
Number of cases	61	44
Number of deaths	34	11
Mortality rate (per cent.)	55·7	25

Of the 119 cases, seventy occurred before the introduction of Rh-negative blood and forty-nine afterwards. Of the seventy cases occurring before, forty-three died—a mortality rate of 61·4 per cent. Of the forty-nine occurring after, sixteen died—a mortality rate of 32·7 per cent. However, since an attempt is being made to determine the value of transfusion therapy, the nine cases before, and five after, who died before transfusion could be given, must be excluded. When the transfused cases only are considered, the mortality rate is seen to have dropped from 55·7 to 25 per cent. (table 2) With the introduction of Rh-negative blood, therefore, the mortality rate has been more than halved. That progress has been made is undoubted, but that one in four of the treated cases has died is nevertheless disquieting. All the infants received at least one transfusion, and they did not die as a direct result of anaemia. That liver dysfunction plays a part seems now clear (Parsons, 1946) and is emphasized by the fact that of the twenty-five cases of congenital haemolytic anaemia admitted during the same period only two died, both of them before the use of Rh-negative blood. There have been no deaths in that condition since. In congenital haemolytic anaemia there is usually evidence of greater blood destruction than in icterus gravis, and it is the obstructive type of jaundice present in the latter which is the cause of the much higher mortality. Wiener (1946) considers that the two conditions are caused by different antibodies, an agglutinin causing icterus gravis and a glutinin (blocking antibody) causing haemolytic anaemia. The former, according to his theory, is the one responsible for the liver damage and the latter causes only destruction of red cells. If this is so, one would expect from the variety of the clinical findings in many cases that both antibodies would be present. There are few cases of icterus gravis which, if they recover, do not become anaemic, and most cases of congenital haemolytic anaemia have some jaundice in the early stages of the disease. Unfortunately the blocking antibody can only be demonstrated in the presence of the agglutinin by a difference in titre, so that the presence of both cannot often be shown. Whether Wiener's serological classification of the disease will be confirmed and accepted remains to be seen (*Lancet*, 1946) but from the clinical point of view there are two extremes of the disease, as seen in a children's hospital. At one end severe jaundice with little anaemia, and at the other severe anaemia with little or no jaundice. The majority of cases, however, seem to fall between the two extremes. It has been suggested that transfusion as soon as possible after the diagnosis has been made, either on clinical or serological grounds, may improve the prognosis. In view of the part which liver dysfunction appears to play, there seems no valid reason for thinking that Rh-negative cells or plasma will have a very beneficial effect on the prognosis unless anaemia is also present. It may, of course, have some effect in diminishing the haemorrhagic tendency which is often present, but that would not appear to be sufficient reason for its routine use unless the blood picture also indicates that transfusion is necessary. Terminal infection, mainly bronchopneumonia, was found in nine out of the eleven infants who died (table 2). Although these children are not premature by weight, their resistance to infection is low, as would be expected from their disordered metabolism, and this factor should be considered during their treatment.

The discovery of the Rhesus factor has certainly contributed greatly to the knowledge of serologists and geneticists, but the greatest advances so far have been on the purely scientific side. Broman (1945) has pointed out that nothing more than transfusion with Rh-negative blood has been introduced for the benefit of the child. Caesarean section before term does not appear to have met with the success hoped for, and the prevention by other means of this disease, which is unique in its etiology, still seems remote.

Summary

1. In the differential diagnosis of haemolytic disease of the newborn, a history of previous stillbirths is of some importance in indicating maternal

sensitization to the Rhesus factor, but a history of previous abortions is of none.

2. Other conditions may simulate the disease entity of icterus gravis neonatorum. Brief histories of three cases have been presented.

3. Since the introduction of transfusion with Rh-negative blood, the mortality rate in all cases of icterus gravis neonatorum has fallen from 61·4 to 32·7 per cent., and in cases receiving one or more transfusions from 55·7 to 25 per cent.

4. The fact that the mortality is still so appreciable is due to the hepatic dysfunction which is present in the more severe forms of the disease.

I wish to thank Prof. D. F. Cappell for much valuable advice and the gift of sera. Dr. Stanley Graham, in whose wards the study has been made, has been a constant source of encouragement, and Dr. G. L. Montgomery has given me all possible help in his pathology department. Many of the cases were in Prof. G. B. Fleming's wards and I wish to thank him for allowing me to have access to their records and for continued interest.

References

Boorman, K. E., Dodd, B. E., and Mollison, P. L. (1944). *J. Obst. Gynaec. Brit. Emp.*, **51**, 1.
Broman, B. (1945). *Acta Paediat.*, **34**, 158.
Eden, T. W., and Holland, E. (1937). *A Manual of Obstetrics*. 8th ed., London, 210.
Gimson, J. D. (1943). *Brit. med. J.*, **2**, 293.
Hampson, A. C. (1929). *Lancet*, **1**, 429.
Lancet (1946). (Annotation.) **2**, 242.
Levine, P. (1941). *Amer. J. clin. Path.*, **11**, 898.
Mollison, P. L. (1943). *Proc. roy. Soc. Med.*, **36**, 221.
Mourant, A. E. (1945). *Nature*, **155**, 542.
Munro Kerr, J. M., et al. (1933). *Combined Textbook of Obstetrics and Gynaecology*. 2nd ed., Edinburgh, 225.
Parsons, L. G. (1946). *J. Obst. Gynaec. Brit. Emp.*, **53**, 1.
Race, R. R. (1944). *Nature*, **153**, 771.
Report of Medical Officer of Health, City of Glasgow. (1943). p. 12.
Rolleston, H. D. (1920). *Practitioner*, **104**, 1.
Wiener, A. S. (1946). *Amer. J. Dis. Child.*, **71**, 14.

THE TREATMENT OF ERYTHROBLASTOSIS FOETALIS

BY

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Since 1941, when Levine, Katzin, and Burnham demonstrated that haemolytic disease of the newborn may be due to immunization of the mother by the Rhesus antigen, the investigations of Wiener and his colleagues (1946), and of Coombs, Mourant, and Race (1945), have seen prediction brilliantly fulfilled. The most recent aid in haematological diagnosis has been the anti-human globulin rabbit serum of Coombs et al. (1945), with which non-specific sensitization of the baby's cells by a maternal antibody may be shown.

The mechanism of the production of erythroblastosis is now understood, at least in the majority of cases, but attention has been focused on the etiology to a greater extent than on the treatment of the condition. There remains a large field for investigation into the best means, firstly, of treating the haemolytic aspect, and, secondly, of preventing the late sequelae of the disease. Among the latter, hepatosplenomegaly (Drummond and Watkins, 1946), kernikterus, and mental defect are known to occur, and it is probable that other conditions, notably spastic diplegia, will be shown on further investigation to be part of the aftermath of so-called erythroblastosis foetalis.

Treatment at the present time is properly concerned with the transfusion of Rh-negative blood, providing the baby with a vehicle for oxygen-carrying which should be immune from the influence of the agglutinin causing haemolysis of its Rh-positive cells. Preservation of life is the primary consideration, and the maternal agglutinin present in the baby is left to take care of itself. It is this antibody, however, present either in its complete or ' incomplete ' form, which is responsible for the haemolysis and the later phenomena, and Wiener (1946) has suggested that the incomplete form may be more potentially dangerous than the complete antibody.

Only rarely has the anti-Rh agglutinin been demonstrated in the child's serum (Coombs et al., 1946) although Baar (1945) has shown that the incomplete antibody is present in roughly 50 per cent. of babies in a small series of cases. Wiener has postulated different molecular sizes for complete and incomplete agglutinin, and there is agreement that, having been called forth in the mother, they pass across the placental site to exert their effect on the baby's cells. Thereafter little is known of their fate, but they presumably may last in the baby's circulation and tissues for two to three weeks, as do other immune bodies.

Although maternal antibody is not often directly demonstrable in the foetal serum, its presence may be inferred from the fact that at birth the foetal cells are sensitized, as shown by the anti-globulin serum test. How long its presence continues is not known, and so the blood of affected babies was investigated to ascertain how long antibody survives in sufficient quantity to sensitize the red cells. It is possible that some sensitized red cells will outlast the presence of ' free ' antibody in the serum.

Investigation

Ten consecutive babies admitted to this hospital with erythroblastosis were investigated. In every case there was a parental Rh incompatibility and a maternal agglutinin was present. The red cells of each baby were found to be sensitized on admission, and direct sensitization tests were performed at weekly intervals until the cells gave a negative reaction. The results are shown in fig. 1. It will be seen that in nine out of the ten cases the antibody had ceased to sensitize the cells after twenty-eight days, and that in the last case the test had become negative after a further week.

There was some superficial relationship between the maternal antibody titre and the duration of foetal sensitization, and this is illustrated in fig. 2. In all cases the antibody titre was estimated on the fourteenth day after parturition, when the titre is normally

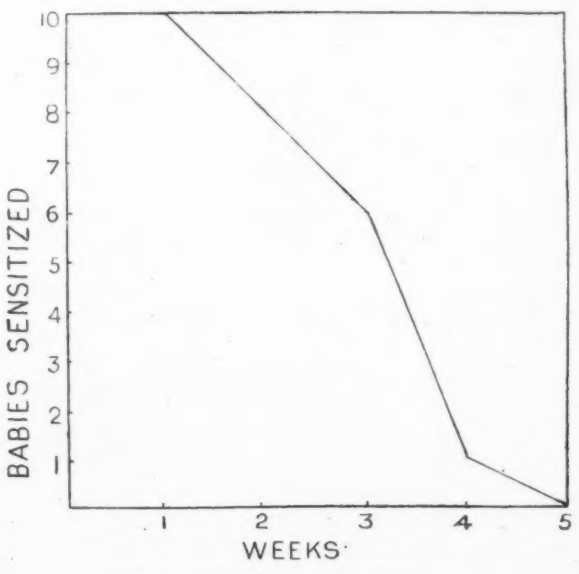


FIG. 1.—Duration of sensitization.

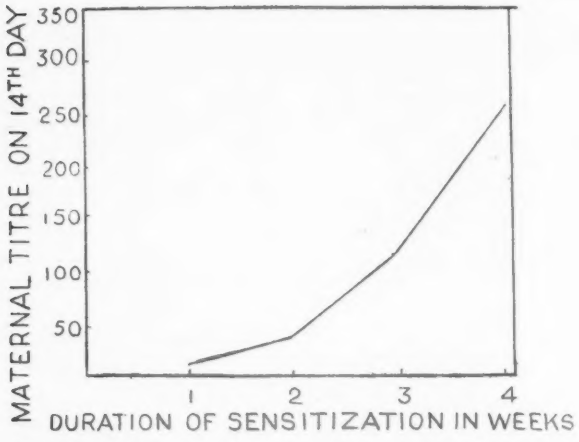


FIG. 2.—Maternal titre in relation to duration of sensitization.

at its highest. It is not intended to draw any conclusions from such small figures, but the findings are in contrast to the lack of correlation between maternal antibody titre and the clinical severity of erythroblastosis.

From this investigation it appears that maternal antibody cannot be demonstrated in the foetal serum, either directly or indirectly, later than a month after birth. After the antibody has disappeared the haemolysis should cease and recovery in the blood picture should take place, but this improvement notoriously does not occur in many cases. The following case illustrates this failure.

Case 1. Baby P., the second child of healthy parents, was admitted jaundiced at three days old on June 2, 1946, with clinical erythroblastosis. The first child was normal. On admission the red cell count was 1,620,000 per c.mm., haemoglobin 30 per cent. (Sahli) or 4·2 g. per 100 c.cm. The white cells numbered 24,000 per c.mm. and late normoblasts 19,000 per c.mm., reticulocytes 11 per cent. The red cells were sensitized, but no agglutinin was demonstrable in the foetal serum. The child was group A CDe cde, the father group A CDe cde, and the mother group A cde cde with an anti-CD titre of 8 on the fourteenth day after birth. The subsequent blood history of the baby is shown in table 1.

How much longer this child will need blood replacements remains to be seen. He has already had nearly twice his birth volume of whole blood, and the count is still only about half what it should be.

In cases similar to this one, an actual marrow dysplasia appears to be present, and in several such children a series of marrow counts was made in parallel with the blood counts. A typical example is the following, only the more important of the many investigations carried out being included.

Case 2. Baby M., a second child, was admitted with erythroblastosis on February 23, 1946. The blood group was A CDe cde, and the maternal antibody titre on the fourteenth day after birth was 256. Between the date of admission and April 1, 1946, the child received eight transfusions, totalling 750 c.cm. of Rh-negative blood, or more than twice his own blood volume. In spite of this the blood count on April 2, was still falling, although no Rh-positive cells were present, and, due to donor's blood, the peripheral blood group was O (Cathie, 1946). At this stage the marrow was counted and was found to contain only 2 per cent. of late normoblasts and 0·5 per cent. of intermediate normoblasts. In view of this hypoplasia, further transfusions were withheld to see if the degree of anaemia would cause the marrow to undergo some hyperplasia (table 2).

TABLE 1

Date	Red cells per c.mm. (millions)	Treatment and condition
2.6.46	1·6	Transfused with 120 c.cm. of Rh-negative blood.
5.6.46	4·3	
9.6.46	3·4	Transfused with 80 c. cm. of blood.
10.6.46	5·03	
11.6.46	4·5	The jaundice had disappeared.
22.6.46	4·1	The cells were still sensitized.
30.6.46	3·0	The cells were no longer sensitized.
7.7.46	2.2	Transfused with 80 c.cm. of blood.
13.7.46	2·7	
15.7.46	2·1	Transfused with 90 c.cm. of blood.
20.7.46	3·3	
27.7.46	2·5	Transfused with 150 c.cm. of blood.
30.7.46	4·9	
7.8.46	2·9	

TABLE 2

Date	Red cells per c.mm. (millions)	Marrow nucleated reds (per cent.)
2.4.46	4·2	2·5
25.4.46	3·6	
27.4.46	2·6	
30.4.46	3·1	13·0
2.5.46	3·2	
16.5.46	3·3	24·0
20.6.46	4·5	26·0

Transfusion

These two cases raise a series of pertinent questions concerning the transfusion of blood. They are not isolated, but cases representative of the majority of the babies admitted to this hospital with erythroblastosis. The more important questions are: at what level of anaemia shall blood be given, how much shall be given, at what speed and by what method, and, lastly, what type of blood?

Whitby and Britton (1946) say that twelve days after birth the red cell count is 5 to 5½ millions, although personal experience would place the count somewhat lower. Chuinard, Osgood, and Ellis (1941) give the average count as 4·6 million, with a normal range from 5·8 to 3·4 million. If this low figure of 3·4 million is taken to be the lowest limit of normality, then any count below it in the neonatal period indicates anaemia, and correction of this anaemia

when the baby is first seen in the stage of active haemolysis, and later when a varying number of donor cells are present, calls for somewhat different treatment.

In the early stages of erythroblastosis there is usually some degree of anaemia ; many of the red cells are reticulocytes, while others are basophilic macrocytes. Normoblasts may be present in small numbers or up to 100,000 or more per c.mm. and the general blood picture suggests deficiency of oxygen-carrying powers. Experience has shown that the anaemia is progressive, and there is little point in withholding immediate transfusion of Rh-negative blood. Enough should be given to bring the red cell count up to about 4·5 million. Theoretically these Rh-negative cells should be unaffected by Rh-agglutinins and should survive for a normal time apart from obsolescence. In many cases, however, continued haemolysis, after more than enough Rh-negative cells have been given entirely to replace the circulation, suggests that other factors apart from agglutinins and normal wear and tear are involved in the production of anaemia.

After the initial transfusion, the blood count usually falls slowly to a level when more blood is indicated, but this level is difficult to decide upon. In case 2, quoted above, the count was allowed to fall to 2·6 million, after which it rose of its own accord to within normal limits. Probably about 2·5 million is the lowest to which the count should be allowed to fall, on account of the possible dangers of tissue damage due to anoxaemia, and at this level a further transfusion should be given.

As a general principle the count should not be raised to 5 million, for two reasons. Firstly, the count is not maintained at this level, and the resulting haemolysis may throw an added strain on an already potentially damaged liver. Secondly, the bone marrow must be assisted in every way to produce its own cells, and while a small blood transfusion may act as a stimulus to production a normal peripheral count will tend to allow the marrow to lie fallow.

The majority of babies seem to fix for themselves a rather low red cell count, usually between 3 and 3·5 million, and on this they thrive and put on weight. Above this level they lyse the peripheral red cells and return to their individual level. Therefore enough blood should be given after the initial transfusion to bring the count to about 3·5 million as often as it has fallen to 2·5 million. Many babies have been treated on these lines and have done uniformly well, the count eventually stabilizing in the region of 3 million for some weeks before starting to rise slowly towards the figure of 4·5 million.

The following case of affected twins shows that low blood figures may be maintained without exciting attention. The male child was a case of moderate erythroblastosis, while the female was apparently clinically unaffected.

Case 3. Baby John S., was born on June 2, 1946, and admitted as a case of clinical erythroblastosis on the sixth day after birth. His group was B CDe cde. The mother was B cde cde, and the father O CDe CDe. The female twin's group was O CDe cde. The red cells of both twins were sensitized. After a stormy blood history, in which several transfusions were necessary, improvement in the boy's condition started (table 3).

TABLE 3

Date	Red cells per c.mm. (million)		Treatment and condition
	Boy	Girl	
12.7.46	3·3		Cells of both babies now gave a negative sensitization test, and both were agglutinated by maternal serum to a titre of 1 in 256.
17.7.46	2·8	3·6	Boy transfused with 60 c.cm. Rh-negative blood.
29.7.46	3·3	3·0	
8.8.46	3·9	3·4	

Comment

There is no doubt that here both twins were affected. Both twins' cells were sensitized, and the maternal serum agglutinated the cells of each to the same titre. It is not clear why the boy manifested erythroblastosis clinically, while the girl had a transient so-called physiological jaundice which had disappeared before her brother was admitted to hospital. And while the blood count of the boy was considered low and he was not thriving, the girl continued to put on weight ; it was not until her blood group was checked that her count was found to be lower than that of the brother, who was receiving all the attention.

The amount of blood to be given to obtain a desired rise may be calculated from the red cell count or the haemoglobin percentage, and, as the anaemia is normocytic, either may be used. The blood volume in infants is assumed to be between 40 and 50 c.cm. per lb. of body weight, and to err on the safe side the lower figure of 40 may be used for calculation. Gimson (1943), using haemoglobin levels, gives the formula

$$\frac{\text{desired percentage rise in haemoglobin} \times \text{blood volume}}{100}$$

for estimating the amount of blood to be transfused. As, however, hyperbilirubinaemia is so frequent in erythroblastosis and gives rise to such faulty haemoglobin readings, blood amounts based on the red cell count are preferred. Using the red count the amount of citrated donor blood to be transfused is given by the formula

$$\frac{\text{desired count} - \text{actual count}}{\text{desired count}} \times \text{blood volume.}$$

The formula is not mathematically correct, but works in practice. For instance, suppose it is desired to raise a count of 3 million to 4 million. The desired

count of 4 million minus the actual count of 3 million is 1 million. This, divided by the desired count of 4 million, gives ¼. If the baby weighs 7 lb. the approximate blood volume will be 7 × 40, or 280 c.cm., so that the necessary amount of blood is ¼ of 280, or 70 c.cm.

It has recently been shown that some donor cells may survive after transfusion as long as 120 days, after which they are no longer demonstrable. When taken from the donor these cells will be in all stages of maturation, and, while the longest surviving cells may reasonably be assumed to be the most recently produced by the donor, the older transfused cells will have a shorter life. If the graph of days and number of cells surviving is a straight line, there will be a small reduction daily in the recipient's red cell count. In case 2, none of the child's own cells remained, all the circulating red cells being donor cells, which brought the blood count to 5 million. In such a case a daily fall of, roughly, 1 per cent. of haemoglobin would be expected if normal obsolescence occurred with no replacement from the recipient's marrow. That other factors are involved in the production of the anaemia is shown by the fact that more than double the blood volume of whole Rh-negative blood had been given to this baby in six weeks and the blood count was then only about half of what it should have been. Differential cell survival estimations were not necessary, as, had all the Rh-negative cells transfused survived, the peripheral blood count would have been in the region of 12 million.

Blood may be transfused by cannulization of a vein, or directly into a scalp vein with a small intravenous needle. For the initial large transfusion the blood is best given slowly, by means of a cannula tied into a vein, at the rate of 15–20 c.cm. per hour. The total volume of blood to be transfused is seldom more than 200 c.cm., so that it may conveniently be given during the course of a day. This slow rate allows the baby to deal with the excess of fluid by normal excretion. During the transfusion the baby's spleen may be felt to enlarge, and presumably becomes engorged with blood, and for this reason a blood count to check the result of the transfusion is best delayed for twelve hours, when the spleen has shrunk and a representative count may be obtained.

There is a limited number of veins in the infant which can be cannulized, and transfusions subsequent to the initial one may be given into a scalp vein. The amount of blood to be given for maintenance is usually small, and the method results in a considerable saving of the time of the operator and that of the nursing staff. It is preferred to the marrow infusion method of Gimson (1944) because of the risks of sepsis attaching to the latter.

The apparatus necessary for a scalp vein transfusion is a 20 c.cm. syringe and a two-way adaptor connecting to a blood reservoir on the one hand and a Luer-Kaufman syringe on the other. The Luer-Kaufman syringe is of about 2 c.cm. capacity and has a side arm half way along the barrel; the plunger has a small metal chain connecting it to the barrel, so that pressure through the side arm cannot expel the plunger. After washing the apparatus through with saline, blood is propelled from the 20 c.cm. syringe through the connecting rubber tubing into the small syringe. The small syringe is then emptied, and sterile saline taken into it so that the plunger stops short of the blood-containing side arm.

The largest and straightest scalp veins are usually found above the ear, and one of these is entered with a small needle on the Luer-Kaufman syringe. When blood is seen entering the syringe the plunger is drawn back past the side arm, and gentle pressure on the 20 c.cm. syringe allows blood to flow into the vein. By this technique blood may be given at the rate of 60 to 80 c.cm. in fifteen to twenty minutes.

The potential drawback to the method is that the rapid increase in circulating volume may embarrass the recipient's heart action, although very many transfusions have been given without untoward effects. In view of this possibility, however, latterly concentrated cells have been given, concentration being achieved by removing the supernatant plasma after standing the bottle of blood for between twelve and twenty-four hours.

Economic and sociological factors lend weight to the advantages of scalp vein transfusion. Firstly, it is often three months or longer before erythroblastotic infants can be released from strict supervision, but to keep every affected baby in hospital for this length of time would be impracticable. Control of the blood and clinical conditions can be maintained while they are out-patients, and a small transfusion may be given as necessary, the baby being allowed home after a rest of an hour or so. Secondly, erythroblastosis usually occurs in second and later children, which means that there are other children at home needing maternal care, and the admission to hospital of a nursing mother while her baby is given a formal transfusion throws a strain on the home life and the indulgence of the neighbours.

The standard treatment of Rh incompatibility is the transfusion of Rh-negative blood. As the baby's serum contains anti-Rh agglutinin derived from the mother, which will react with Rh-positive cells, the treatment is essentially sound, and consists in replacing lysed blood by inert cells until such time as the agglutinin is no longer active. The suggestion has frequently been made that Rh-positive blood should be given in order to be agglutinated by the antibody, in the hope that thereby the antibody would be more rapidly removed from the circulation.

Investigation. In order to examine the possibilities of this suggestion the following experiments were carried out. Unsensitized CDe CDe cells were lysed by alternate freezing and thawing, and the stroma, after being centrifuged down, was treated with anti-CD serum. The titre of the serum after incubation with the stroma fell from 1 in 32 to 1 in 4, showing that the stromal antigen was still capable of absorbing agglutinin. CDe CDe cells were next treated with homologous antibody at 37° C. for two hours. They were then washed three times in saline to remove all trace of agglutinating serum, and were resuspended in saline. After freezing and thawing

to lyse the cells, the stroma was removed by centrifuging. The supernatant fluid was found to agglutinate CDe cells, showing that some antibody had been freed from the lysed red cells.

These experiments indicate that Rh-positive blood should not be given in erythroblastosis, as, although some of the agglutinin will be retained on the cells and stroma, some will be released from the cells when they are lysed and will be free to act upon further Rh-positive cells, so that the antibody comes to act almost as a catalyst.

A further suggestion with regard to treatment is that where a pregnant woman is known to have antibodies the infant should be exsanguinated at birth, the circulation being replaced by inert Rh-negative blood. On theoretical grounds such treatment is not likely to be successful, apart from its difficulties and dangers. The foetus is subject to the action of the maternal antibody for the whole nine months of pregnancy, during which time much of the fixation of the antibody in the tissues should have taken place. As was seen in the sensitization investigation reported above, the antibody lasts in the infant only a short time after birth, the longest period being for a month. Thus the antibody can act for a total period of ten months, and the prospects of improved results by cutting this time down to nine months must be slight, while the heroic measure of exsanguination cannot be without risk. The distressing sequelae of erythroblastosis, such as kernikterus and mental defect, have probably been determined during intra-uterine life, but exsanguination theoretically should help the condition of haemolytic anaemia by removing circulating antibody. But that the anaemia is not due entirely to antigen-antibody reaction is shown by the cases in which there is clear evidence that not only Rh-positive cells are lysed, but that Rh-negative cells also disappear from the circulation, sometimes almost as fast as they can be transfused.

Weaning of erythroblastotic infants on account of the high titre of antibody often present in the maternal milk has been recommended. A few experiments have been made in which high-titre Rh-antibody was drunken, and in no case has antibody been demonstrable in the blood thereafter, either by direct or sensitization tests. The anaemic child is notably susceptible to infection, and the weaned child even more so, and the theoretical disadvantages of breast feeding are so overwhelmingly outweighed by the practical advantages that the suggestion of weaning cannot be supported as long as breast feeding is possible.

Comment

Some cases of erythroblastosis make an uneventful recovery after one transfusion, while others are so mild that no treatment other than expectant is necessary, as, for example, the untreated twin in case 3. These are rare, however, and the majority of cases call for more intensive treatment. The foregoing remarks on this treatment are the conclusions drawn from an analysis of the last 38 cases of Rh incompatibility seen in which a maternal antibody was present. There is a small group in which no incompatibility or antibody can be shown but which in every other respect have erythroblastosis, and in these cases efforts to maintain a higher blood level by transfusion have been more successful than in the demonstrable incompatibility cases.

Excluding those infants who were admitted moribund, and who usually died before treatment could be instituted, there was no case of sudden death in the series. This may have been due to the close supervision that was maintained over all the children until their blood counts stayed spontaneously within normal limits, but, unlike the acute haemolytic crises of the Lederer type of anaemia, the fall in the blood count in erythroblastosis is gradual and progressive and an impending dangerous degree of anaemia can usually be foreseen and rectified.

Blood transfusion is at present the only form of treatment available and appears to correct only the anaemic aspect of the disease. Kernikterus, spasticity, and many other afflictions which will doubtless be shown to have their origin in Rh incompatibility, do not seem to be averted by transfusion. In the light of the recent work of Drummond and Watkins (1946), a ten-year follow-up would appear to be necessary before any reliable figures of the incidence of sequelae can be obtained.

Jaundice may be haematogenous or hepatogenous in origin. It has been suggested that liver damage and not haemolysis is the cause of central nervous disease, and the blood and liver components of the disease syndrome have come to be regarded almost as separate entities. It is impossible to subdivide the syndrome into clear-cut compartments in this fashion. Kernikterus can occur with no history of jaundice, while the worst jaundiced babies may never show any sign of nervous involvement. That the anaemia is based on a deeper pathology than a mere intravascular haemolysis is shown by the marrow depression present in so many infants, and it is reasonable to suppose that the erythroblastosis syndrome is, in fact, the result of a series of widespread antigen-antibody reactions in the various tissues, any or all of which may be affected. The immediate effects and late sequelae are merely manifestations of localized tissue damage. That not all the damage is irreversible is shown by the occasional unblocking of blocked bile ducts and by the recovery of the bone marrow hypoplasia under treatment.

It should be borne in mind that blood transfusion is only a replacement therapy. As long as incompatible matings occur, erythroblastosis will be seen, and eventually the ideal treatment of the condition must be its prevention by fixation or elimination of the maternal antibody as it is formed. But until all pregnant women can be accurately blood-typed such a prophylactic ideal, even if there were any method of dealing with the antibody, is unattainable, and for the affected children transfusion of Rh-negative blood must continue as the treatment of choice.

Summary

The indications for and methods of giving blood to erythroblastotic babies are discussed and described. Illustrative cases are cited.

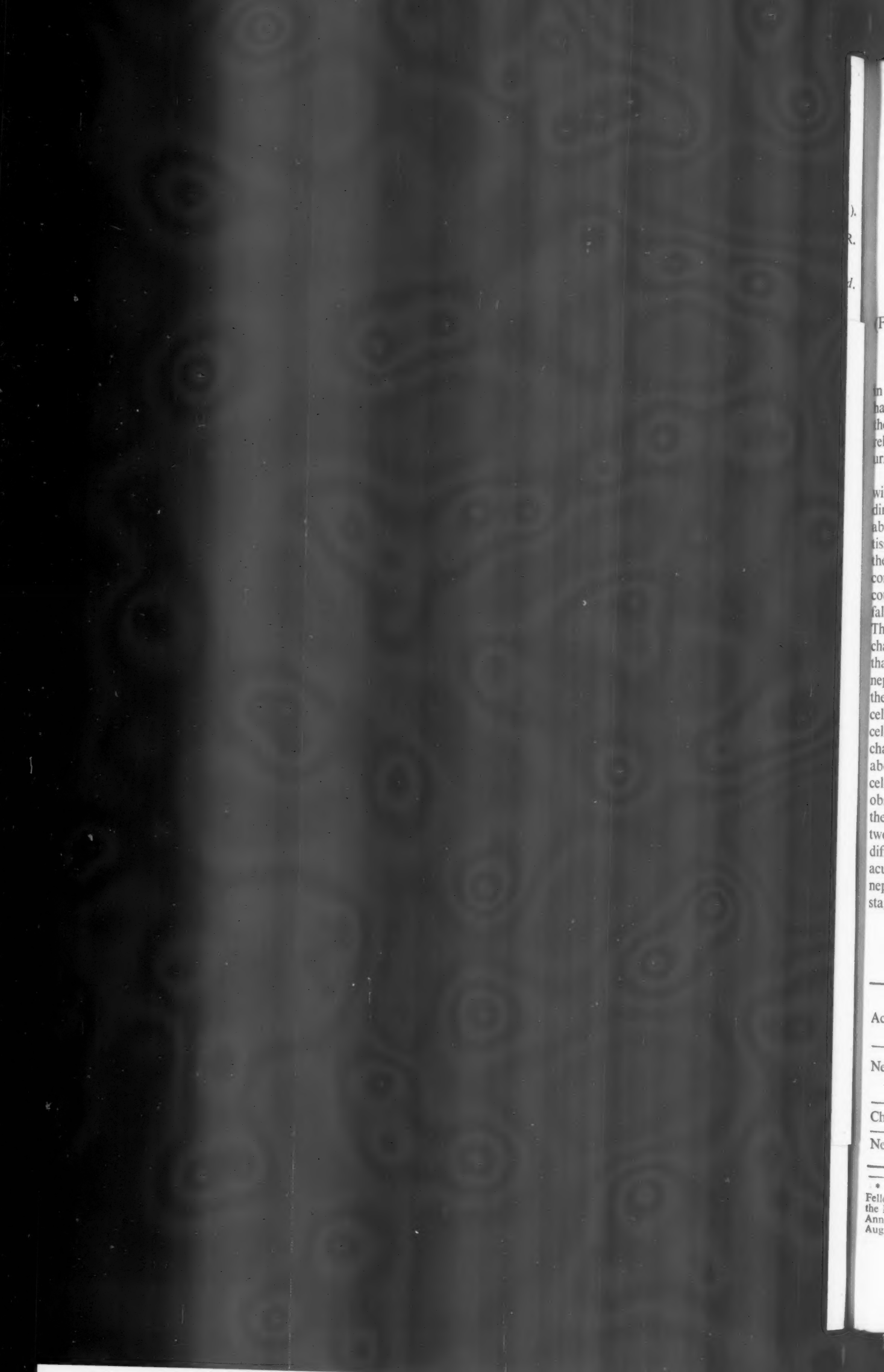
Experimental work is reported to show, in cases of erythroblastosis: (a) the duration of sensitization of foetal red cells by maternal antibody; (b) that the transfusion of Rh-positive blood is contra-indicated; (c) that the dangers of feeding breast milk containing atypical antibodies have been over-estimated.

I am indebted to the physicians of the Hospital for Sick Children, Great Ormond Street, London, for access to their cases, and to Dr. A. D. Barlow for demonstration of transfusion techniques.

References

Baar, H. S. (1945). *Nature*, **155**, 789.
Cathie, I. A. B. (1946). *Lancet*, **2**, 418.
Chuinard, E. G., Osgood, E. E., and Ellis, D. M. (1941). *Amer. J. Dis. Child.*, **62**, 1,188.
Coombs, R. R. A., Mourant, A. E., and Race, R. R. (1945). *Lancet*, **2**, 15.
—— —— —— (1946). *Ibid*, **1**, 264.
Drummond, R. J., and Watkins, A. G. (1946). *Brit. med. J.*, **1**, 984.
Gimson, J. D. (1943). *Ibid.*, **2**, 293.
—— (1944). *Ibid.*, **1**, 748.
Levine, P., Katzin, E. M., and Burnham, L. (1941). *J. Amer. med. Ass.*, **116**, 825.
Whitby, L. E. H., and Britton, C. J. C. (1946). *Disorders of the Blood*. 5th ed., London, p. 337.
Wiener, A. S. (1946). *Amer. J. Dis. Child.*, **71**, 14.

The Publishers regret that, owing to the difficulty of obtaining sufficient supplies of art paper, it will be necessary for the present to print the text of the *Archives of Disease in Childhood* on a lighter paper and to reserve the art paper for half-tone illustrations in which fine detail has to be shown. This is an emergency measure, and it is hoped soon to return to normal conditions.



THE PLASMA VOLUME IN NEPHRITIS*

BY

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During a previous investigation it was found that in certain types of nephritis serial red cell counts and haemoglobin estimations done during the course of the disease revealed a fluctuation which was closely related to the degree of oedema and to the volume of urinary excretion (MacArthur, 1942).

During the phase of recovery in acute nephritis, with the onset of diuresis and the consequent diminution in oedema, the red cell count rises by about 700,000 per c.mm., and when the excess of tissue fluid has been excreted and diuresis subsides the red cell count returns to its previous level. In contrast, in the nephrotic syndrome the red cell count rises with increasing oedema and oliguria, and falls sharply during diminishing oedema and diuresis. The haemoglobin shows similar and proportionate changes. These characteristic fluctuations suggest that the mechanism of diuresis and recovery in acute nephritis with oedema is quite different from that in the chronic nephrotic type. Changes in the red cell count, haemoglobin content, and plasma/red cell ratio, however, do not necessarily indicate changes in plasma volume, for they may be brought about by alteration in the number of circulating red cells. In an attempt to determine whether the observed changes were, in fact, due to variation in the plasma volume in these types of nephritis, forty-two plasma volume estimations have been done at different stages of the disease in twelve patients with acute nephritis and five patients with nephrotic nephritis. The number of estimations in each of the stages is shown in table 1.

TABLE 1

DISTRIBUTION OF PLASMA VOLUME ESTIMATIONS

Acute nephritis 25	Acute stage with oedema	9
	Stage of diminishing oedema	9
	Oedema-free stage	7
Nephrotic syndrome 17	Stage of increasing oedema	8
	Stage of diminishing oedema	4
	Oedema-free stage	5
Chronic haemorrhagic nephritis		11
Nephrosclerosis		5

In addition, eleven plasma volume estimations were carried out in six cases of chronic haemorrhagic nephritis, the only form of the disease in which true anaemia is consistently found, and five in nephrosclerosis.

Methods

Complete haematological and urinary examinations were done on each patient at weekly intervals. The body weight and urinary output were measured daily; the temperature of the ward was fairly constant. The plasma volume was estimated by the dye method of Keith, Rowntree, and Geraghty (1915) as modified by Hooper et al. (1920) and Graff and Clarke (1931). Four cubic centimetres of a 1 per cent. solution of Congo red was injected into an arm vein, and after four minutes 8 c.cm. of blood was taken and mixed in a centrifuge tube containing 2 c.cm. of a 1·1 per cent. solution of sodium oxalate. The plasma was separated by centrifugalization at 3,000 revolutions per minute for 30 minutes, and the dye concentration estimated by the Bürker compensating colorimeter.

Dawson et al. (1920) tested a large series of dyes for use in plasma volume determinations and found that vital red, Congo red, and the blue dye, TI824, were equally efficacious. Others (Robinow and Hamilton, 1940; Gregersen, 1938) have confirmed their work. The blue dye, TI824, has the disadvantage that a higher concentration is required in the blood to give a suitable colour for matching, and it sometimes gives the patient an unhealthy appearance. On the other hand it has a different absorption spectrum from haemoglobin, and so an accurate estimation can be made in the presence of slight haemolysis when a spectrophotometer is available for the colorimetry. It has no advantage over the earlier dye, Congo red, unless the colorimetry is done with a spectrophotometer (Gregersen, 1938). After trials with both spectrophotometer and compensating colorimeter for the dye method of plasma volume estimation, Weech et al. (1937) preferred the compensating colorimeter as being just as accurate as the spectrophotometer and much less time-consuming. A spectrophotometer was not available when the present series of estimations was made, but no trouble was experienced from haemolysis, and the compensating colorimeter proved entirely satisfactory.

Published reports show that some investigators in this country still used 1·6 per cent. sodium oxalate solution as an anti-coagulant, based on the results of Hooper et al. (1920), although Graff and Clarke (1931) have shown that Hooper's experiments on dogs are not exactly applicable to human beings, in

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whom the correct dilution is 8 c.cm. of blood in 2 c.cm. of 1·1 per cent. sodium oxalate.

Not more than seven blood volume determinations can be made with accuracy on one patient, as the dye thereafter begins to be removed too rapidly from the circulation (Lindhard, 1926).

It is desirable that the subjects under investigation should live in wards or rooms which are maintained at a more or less equable temperature, since it has been shown by Bazett (1938) that two men who lived in a room maintained at 74·5° F. had an increase of blood volume of 6 per cent. after one day, 10 per cent. after two days, and 25 per cent. after three days. The same author, working in America, found the blood volume to be 30 to 40 per cent. higher in mid-summer than in mid-winter.

The Normal Blood Volume

It is generally agreed (Brown and Rowntree, 1928; Bock, 1921) that the normal range of blood volume obtained in adults by the Congo red dye method is 72–100 c.cm. per kg. of body weight, average 88 c.cm. per kg., and of plasma volume 43–59 c.cm. per kg., average 53 c.cm. per kg. Using the blue T1824 the results are rather lower (Gibson and Evans, 1937; Davis, 1942).

There is much less agreement about the standards for children, and no really comprehensive investigation has yet been published. Dreyer and Ray (1911) have shown by exsanguination methods that, in mammals, small young animals have a relatively greater blood volume than larger and older animals of the same species. By analogy it may be assumed that the blood volume of children is relatively greater than that of adults. A summary of the published results in childhood is presented in tabular form (table 2) and from this it will be seen that the blood volume in relation to weight is about 100 c.cm. per kg. during infancy and gradually decreases to reach the adult level at about four years of age.

Before estimating blood volumes in children, three adults were subjected to the test to determine whether our technique gave results comparable to those of other workers. The plasma and blood volumes (table 3) were within Brown and Rowntree's normal range, though the average is rather low and would have been even lower but for the high blood volume in one subject (P.M.) who was underweight for his height.

The Blood and Plasma Volume in Nephritis

Study of the literature shows that different workers have obtained very inconsistent and discordant results in the estimation of the blood and

TABLE 2

THE PLASMA AND BLOOD VOLUME OF NORMAL INFANTS AND CHILDREN

Authority	No. of estimations	Age group	Plasma volume c.cm./kg.	Blood volume	
				c.cm./kg.	Total c.cm.
Bakwin and Rivkin (1924)	25	< 1 yr.	61 (38–72)	101 (71–148)	
Lucas and Dearling (1921)	30	<15 days	59 (42–77)	147 (107–195)	
	11	< 1 yr.	67 (57–78)	109 (90–126)	
Darrow, Soule, Buckman (1928)	52	Birth	50		
		6 mths.	62		
		4 yrs.	50		
Robinow and Hamilton (1940)	20	Newborn		98	
McIntosh (1929)	10	2 mths. to 21 mths.		93 (∓10)	
Brines, Gibson, Kunkel (1941)	9	Birth			300
		1 yr.			600
Schlutz, Morse, Cassels, Iob (1940)	41	Puberty			2,500
	7	14 yrs.	45		
	9	17 yrs.	47		
Seckel (1936)	?	Childhood	50	83 (73–93)	

TABLE 3

THE BLOOD VOLUME IN NORMAL, HEALTHY ADULTS

Name	Age yrs.	Ht. cm.	Wt. kg.	S.A. sq. m.	Haematocrit R.B.C. vol. %	Plasma			Red cells			Whole blood		
						c.cm./kg.	c.cm./sq. m.	Total c.cm.	c.cm./sq. m.	c.cm./c.cm.	Total c.cm.	c.cm./kg.	c.cm./sq. m.	Total c.cm.
T. C.	25	181	72·2	1·90	45·9	41	1,551	2,946	35	1,316	2,500	75	2,866	5,446
A. R.	25	174	63·8	1·76	47·9	40	1,459	2,567	37	1,885	2,359	77	2,799	4,926
P. M.	25	186	69·6	1·92	48·2	51	1,806	3,567	48	1,729	3,319	99	3,592	6,886
Average	25	180	68·5	1·86	47·3	44	1,605	3,027	40	1,643	2,726	84	3,086	5,753

plasma volume in nephritis. Brown and Rowntree (1928) found no evidence of hydraemic plethora in glomerulo-nephritis with oedema, nor did they observe any uniform changes in the blood or plasma volume during diuresis. In nephrosis they found an increased plasma volume unaffected by oedema or diuresis.

Harris and Gibson (1939) also found the plasma volume increased in nephrosis, and considered that there is no consistent change in the plasma volume with variations in oedema, although the results which they publish show in most of their cases a marked fall of plasma volume during oliguria and oedema, and a rise in volume with diuresis and absence of oedema. Many of their patients were anaemic, and so presumably had a superadded infection. They consider that the plasma volume is unrelated to the stage or the type of nephritis and is dependent only on the inter-relationship of serum albumen, nonprotein nitrogen, and degree of anaemia.

Linder et al. (1924) investigated the plasma volume in four patients with nephrotic nephritis with the special object of finding out whether the low plasma protein was due to dilution of the blood. They concluded from their results that the volume of the plasma was either uninfluenced by the presence of oedema, or else that it was actually diminished when anasarca was extreme. Darrow (1926) studied three children with nephritis and oedema and found low plasma volumes during oedema rising to normal after it had disappeared. Waterfield (1931), using the carbon monoxide method, examined five patients with renal oedema and found the plasma volume to be abnormally low during increasing oedema and to rise as oedema disappeared. However, many complicating factors were present in his patients; one had ' severe heart failure,' another had completed a pregnancy only four weeks previously, and in a third the reduction of oedema was obtained by multiple skin punctures. A diminution in plasma volume has been shown to occur in the diuresis induced by salyrgan (Evans and Gibson, 1937).

It is suggested that the failure to obtain consistent results in the investigations quoted above may be due to one or more of the following causes: (1) insufficient differentiation of the type of oedema, e.g. nephritic, nephrotic, cardiac; (2) failure to time the estimations to coincide with rapid increase or rapid decrease in oedema, and to differentiate the two groups in appraising and presenting the results. For example, a patient whose normal weight is 50 kg. and whose weight when oedema is 60 kg., may have a blood volume estimation done when he weighs 55 kg. and has well marked oedema. Such an estimation remains valueless unless it is known whether it was obtained while oedema was increasing to 60 kg. and the disease was active, or while oedema was diminishing and recovery in progress; (3) an insufficient number of plasma volume estimations in some of the series; (4) the presence of complicating diseases or circumstances, and the use of artificial measures, such as multiple skin punctures, to obtain reduction of oedema.

Results

Acute Haemorrhagic Nephritis (Table 4). Twenty-five plasma volume estimations were done on twelve patients with acute nephritis. The results have been separated into three groups for purposes of comparison, namely those done: (1) when the patient was markedly oedematous in the initial stage of the disease and before diuresis had become established; (2) when the oedema was subsiding and there was well marked diuresis; (3) when all oedema had disappeared, diuresis had passed off, and the patient was convalescent.

TABLE 4

PLASMA VOLUME IN ACUTE NEPHRITIS

Name	Age in Years	Stationary oedema: before diuresis		Subsiding oedema: during diuresis		No oedema: after diuresis	
		Total c.cm.	c.cm./ kg.	Total c.cm.	c.cm./ kg.	Total c.cm.	c.cm./ kg.
G. C.	7	865	49			901	51
F. C.	6	986	65	645	43		
R. McP.	4					717	53
A. J.	5	1,083	67			925	57
A. D.	10	1,433	61	1,039	44	1,613	68
R. J.	10					1,474	58
E. G.	8	1,067	57	972	51	1,385	73
R. D.	10	1,573	68	1,190	52		
E. G.	10	1,151	59	978	50		
J. M.	5	882	61	763	53	1,088	76
S. D.	4	869	59	644	44		
G. H.	8			1,024	52		
				996	51		
Averages			61		49		62

The results of plasma and blood volume estimations have been expressed in cubic centimetres per kilogramme of body weight as well as total volume, as this provides a useful means of comparing the extent of the change in volume in children of different age and weight. But a child's weight is, of course, greatly augmented by the mass of oedema, and it would be erroneous to relate the plasma volume to the artificially high weight of a grossly oedematous child. For this reason in each case the ' oedema-free weight,' that is, the lowest weight that the child reached after all oedema had disappeared, was used for calculating the plasma volume per kilogramme. For instance, the child A. D. (table 4) weighed 29·6 kg. on the day of her first plasma volume estimation, 25·1 kg. on the day of the second, and her final oedema-free weight was 23·6 kg., but the volumes of 61, 44, 68, are each calculated on a weight of 23·6 kg. This seems the most useful and reasonable way of arriving at a basis for comparison, although it is realized that the final weight, coming as it does after acute illness with dietetic restrictions, must usually be below the child's normal weight in health. This is the reason why the plasma volume appears high in relation to body weight in all patients except those with nephrosis.

The results show that the plasma volume is not above normal while the child has gross oedema;

that it becomes considerably reduced when the kidney recovers its function and diuresis occurs, and that it returns to normal when the diuresis comes to an end and the fluid balance is restored.

Nephrotic Nephritis (Table 5). Seventeen plasma volume estimations are recorded on five patients with nephrosis. Since this is not an acute disease, and is not usually accompanied by any wasting, the oedema-free weight of these children is not much below the expected weight for age, and consequently the plasma volume related to weight is only slightly above normal during the quiescent phase of the disease.

The average of the results does not demonstrate any consequential change in the plasma volume during the stage of increasing oedema and oliguria, but when oedema is diminishing and diuresis has commenced there is a definite increase in plasma volume. The fact that when urinary output is at its minimum there is no increase in plasma volume and it is considerably raised during the period of diuresis strongly suggests that in nephrotic nephritis it is the change in plasma volume which determines the volume of urinary excretion. It is very difficult to recognize exactly when these children are developing a large accumulation of oedema, since during the active phase of the disease their weight and urinary excretion fluctuate considerably every few days, and it is considered probable that, if the plasma volume estimations shown in the first column of table 5 could be timed accurately to synchronize with a period of rapidly increasing oedema, the volumes obtained would be even lower than those recorded. This is supported by the results obtained in the patient, T. M., in whom the estimations were well timed to coincide with rapid fluctuations of oedema.

TABLE 5
PLASMA VOLUME IN NEPHROSIS

Name	Age in Years	Increasing oedema: oliguria		Diminishing oedema: polyuria		No oedema	
		Total c.cm.	c.cm./ kg.	Total c.cm.	c.cm./ kg.	Total c.cm.	c.cm./ kg.
J. McD.	5	1,158	62	1,402	74	1,154	62
		1,175	63	1,236	66		
T. M.	7	873	49	1,416	80	985	55
		841	47				
		889	50				
I. D.	5	506	42				
W. G.	7		-	1,682	90	950	51
C. McG.	3	728	52			741	53
		775	55			732	52
Averages			52·5		77·5		55

Nephrosclerosis (Table 6). A blood volume estimation has been made on each of five children with nephrosclerosis. They were typically thin, undernourished children and all had been on a restricted diet for variable periods. This explains the high blood and plasma volumes in relation to weight, and is comparable to the findings in healthy subjects who are of spare build (Rowntree, Brown, and Roth, 1929 ; Gibson and Evans, 1937). There is no evidence that there is a significant alteration in total blood volume in this group of patients.

TABLE 6
BLOOD AND PLASMA VOLUME IN NEPHROSCLEROSIS

Name	Age in years	Haemoglobin (% Haldane)	Plasma volume		Blood volume	
			c.cm./ kg.	Total c.cm.	c.cm./ kg.	Total c.cm.
J. C.	6	86	58	742	104	1,318
M. McN.	9	108	60	1,001	109	1,810
J. D.	9	74	62	986	101	1,611
R. L.	10	43	55	988	71	1,263
P. B.	7	58	52	724	79	1,104
Averages		74	57	888	93	1,421

Chronic Haemorrhagic Nephritis (Table 7). Eleven plasma volume estimations on six cases of chronic haemorrhagic nephritis reveal the high relative plasma volume expected in thin, underweight children with anaemia.

The mean height of these children was 125 cm., and their mean weight was 21·2 kg. Had they been normal healthy children with an average height of 125 cm., their average weight would have been 26 kg. (Holt et al., 1933), and from this figure, using the standards of Rowntree et al., we can calculate what the normal plasma and red cell volumes should be:

TABLE 7
BLOOD AND PLASMA VOLUME IN CHRONIC HAEMORRHAGIC NEPHRITIS

Name	Age in years	Haemoglobin (% Haldane)	Plasma volume		Blood volume	
			c.cm./ kg.	Total c.cm.	c.cm./ kg.	Total c.cm.
A. A.	8	64	45	1,019	66	1,494
J. C.	5	44	79	1,302	105	1,736
J. R.	7	72	65	1,823	106	2,981
		80	59	1,662	101	2,847
		75	65	1,831	108	3,033
P. C.	7	70	68	1,230	107	1,934
		76	74	1,334	118	2,118
M. R.	6	58	64	887	90	1,245
		60	70	964	100	1,383
		62	64	889	99	1,372
A. McA.	12	85	48	1,373	84	2,384
Averages		68	64	1,301	99	2,043

Height cm.	Weight kg.	Red blood cell vol. c.cm.	Plasma vol. c.cm.	Blood vol. c.cm.
125	26	910	1,378	2,288

The actual results obtained in these children are:

Height cm.	Weight kg.	Red blood cell vol. c.cm.	Plasma vol. c.cm.	Blood vol. c.cm.
125	21·2	747	1,301	2,048

By comparison of these figures it is at once obvious that the reduction in the red cell count in this group is due to a genuine anaemia, and not simply to haemodilution.

Discussion

In the absence of any reliable and sufficiently comprehensive standard of blood and plasma volumes in normal children, it is not possible to make dogmatic statements about the changes in total blood volume which are found in the different types of non-oedematous nephritis.

In acute nephritis, chronic haemorrhagic nephritis, and nephrosclerosis (tables 4, 6, 7) the malnutrition resulting from dietetic restrictions and the influence of the disease leads to a plasma volume high in relation to body weight, in contrast to the findings in the non-oedematous phase of nephrosis (table 5), a disease in which general nutrition is not seriously affected. It appears, therefore, that the results obtained from plasma volume estimations justify the deduction, made from the previously observed variations in the red cell count in the course of acute nephritis and nephrosis, that the mechanism of recovery in these two diseases is entirely different. This is shown diagrammatically in fig. 1.

In acute nephritis with oedema and before diuresis had commenced, the average plasma volume was 61 c.cm. per kg. of oedema-free body weight, but during diuresis with rapidly diminishing oedema the plasma volumes were the lowest recorded in the whole series, averaging only 49 c.cm. per kg.; and then, some time later, when the water balance of the body had been re-established, the plasma volume had returned to approximately the first level of 62 c.cm. per kg. Patients with acute nephritis do not as a rule arrive in hospital during the phase when the oedema is increasing, and so it had not been possible to make any estimations at this stage but, since this is the time when the kidney function is most seriously affected, it is considered probable that the plasma volume is then increased. It is suggested that in the initial stage of acute nephritis, when water excretion by the kidneys is impaired, fluid is dammed back and the plasma volume rises; the excess water then passes out of the blood stream into the tissues, producing oedema, and as it does so the plasma volume gradually returns to normal. When the kidneys recover their function, fluid is drawn from the blood to eliminate accumulated waste products, the plasma volume is reduced, fluid gradually returns from the tissues to the blood, and in this way oedema is diminished. When accumulated waste products have been eliminated and the excess of fluid in the tissues has disappeared, the plasma volume returns to normal and diuresis ceases.

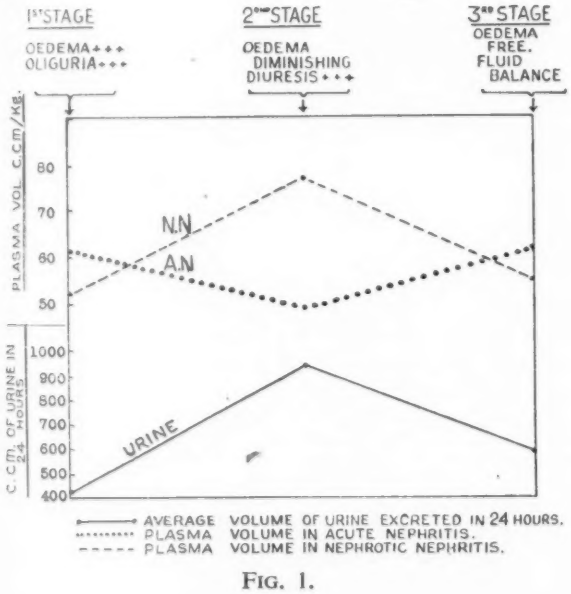

FIG. 1.

In nephrosis the blood volume changes are quite different. Here it was possible to do some of the estimations during a period when the oedema was still increasing and oliguria was more or less marked. At this stage the plasma volumes averaged 52·5 c.cm. per kg. of oedema-free weight. During the second phase, that of diminishing oedema and diuresis, the highest plasma volumes of the whole series were obtained and averaged 77·5 c.cm. per kg., in complete contrast to the lowest volumes of the series obtained during this phase of diminishing oedema in acute nephritis. During the third stage, when oedema had disappeared and diuresis had ceased, the normal value of 55 c.cm. per kg. was obtained. It is suggested that these results provide good evidence that the disease is not due to failure of renal function. Initially fluid passes from the blood into the tissues, and a low plasma volume and oliguria result. During recovery, fluid pours back into the blood, causing subsidence of oedema and an increase in the plasma volume; at the same time the kidney excretes the excess of water in the blood, with resultant diuresis. Finally, when fluid ceases to pass from the tissues to the blood stream in excessive quantity, the plasma volume returns to the normal level and diuresis ceases.

In acute nephritis alteration in the volume of fluid excreted by the kidneys is the cause of the changes in the plasma volume, but in nephrotic nephritis it is the change in the plasma volume that determines the volume of renal excretion.

Summary and Conclusions

1. The plasma volume was estimated in various types of nephritis; twenty-five estimations were made in acute nephritis, seventeen in nephrotic nephritis, eleven in chronic haemorrhagic nephritis, and five in nephrosclerosis.

2. In acute nephritis, in nephrotic nephritis and in chronic haemorrhagic nephritis alterations in the blood and plasma volumes were found.

3. In acute nephritis the plasma volume was considerably reduced during the stage of diuresis and subsiding oedema.

In nephrotic nephritis the plasma volume was below normal during the stage of increasing oedema, and was very considerably above normal during the stage of diuresis, diminishing oedema, and recovery.

4. It is suggested that in acute nephritis alterations in the volume of fluid excreted by the kidneys are

the cause of changes in the plasma volume, but that in nephrotic nephritis changes in the plasma volume determine the volume of renal excretion.

5. In chronic haemorrhagic nephritis there is a low blood volume which is due to reduction in the total volume of circulating red cells.

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References

Bakwin, H., and Rivkin, H. (1924). *Amer. J. Dis. Child.*, **27**, 340.
Bazett, H. C. (1938). *J. Amer. med. Ass.*, **111**, 1,841.
Bock, A. V. (1921). *Arch intern. Med.*, **27**, 83.
Brines, J. K., Gibson, J. G., and Kunkel, P. (1941). *J. Pediat.*, **18**, 447.
Brown, G. E., and Rowntree, L. G. (1928). *Arch. intern. Med.*, **41**, 44.
Darrow, D. C., Soule, H. C., and Buckman, T. E. (1928). *J. clin. Invest.*, **5**, 243.
—— (1926). *Proc. Soc. exp. Biol.*, N. Y., **23**, 740.
Davis, L. J. (1942). *Edinb. med. J.*, **49**, 465.
Dawson, A. B., Evans, H. M., and Whipple, G. H. (1920). *Amer. J. Physiol.*, **51**, 232.
Dreyer, G., and Ray, W. (1911). *Phil. Trans. roy. Soc.*, **201B**, 133.
Evans, W. A., and Gibson, J. G. (1937). *Amer. J. Physiol.*, **118**, 251.
Gibson, J. G., and Evans, W. A. (1937). *J. clin. Invest.*, **16**, 301 and 317.
Graff, S., and Clarke, H. T. (1931). *Arch. intern. Med.*, **48**, 808.
Gregersen, M. I. (1938). *J. Lab. clin. Med.*, **23**, 423.
Harris, A. W., and Gibson, J. G. (1939). *J. clin. Invest.*, **18**, 527.
Holt, L. E., and McIntosh, R. (1933). *Diseases of Infancy and Childhood*. 10th ed., New York.
Hooper, C. W., Smith, H. P., Belt, A. E., and Whipple, G. H. (1920). *Amer. J. Physiol.*, **51**, 205.
Keith, N. M., Rowntree, L. G., and Geraghty, J. T. (1915). *Arch. intern. Med.*, **16**, 547.
Linder, G. C., Lundsgaard, C., van Slyke, D. D., and Stillman, E. (1924). *J. exp. Med.*, **39**, 921.
Lindhard, J. (1926). *Amer. J. Physiol.*, **76**, 497.
Lucas, W., and Dearing, B. F. (1921). *Amer. J. Dis. Child.*, **21**, 96.
MacArthur, P. (1942). *Arch. Dis. Childh.*, **17**, 1.
McIntosh, R. (1929). *J. clin. Invest.*, **7**, 203.
Robinow, M., and Hamilton, W. F. (1940). *Amer. J. Dis. Child.*, **60**, 827.
Rowntree, L. G., Brown, G. E., and Roth, G. M. (1929). *The volume of the blood and plasma in health and disease*. Philadelphia.
Schlutz, F. W., Morse, M., Cassels, D. E., and Iob, L. V. (1940). *J. Pediat.*, **17**, 466.
Seckel, H. (1936). *Arch. Dis. Childh.*, **11**, 21.
Waterfield, R. L. (1931). *J. clin. Invest.*, **9**, 589.
Weech, A. A., Wollstein, M., and Goettsch E. (1937). *Ibid.*, **16**, 719.